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INFANTILE CEREBRAL PALSY

A sociomedical enquire carried out in the county of Østfold in Norway 1954-1955

BY

BJARNE ANDERSEN

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THE COUNTY OF ØSTFOLD

IN NORWAY

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By

BJARNE ANDERSEN

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FOREWORD

Work for the benefit of children suffering from cerebral palsy was started in Norway in 1950. The following paper is a report of a survey made in a section of Norway, Østfold county. The aims of this study were first, to find out how frequently cerebral palsy occurs among children in Norway, second, to try to discover what problems of a sociomedical nature are encountered in the treatment of this condition, and third, to obtain some impression of the extent of these problems.

The enquiry was carried out in part while I was senior assistant in the Children's Department, Oslo City Hospital, Ullevål (head, Dr. R. Rinvik), and partly during my period as junior assistant at the Children's Clinic, Norwegian State Hospital (head, Professor L. Salomonsen).

It was expected that a survey of this nature would be a helpful contribution to the work of the *Norwegian Cerebral Palsy Association.* This association, under its chairman (later secretary) *Mr. Kjell Boysen,* helped in the planning of the work and granted financial aid.

The study was made in the county of Østfold, where the Østfold branch of *Norske Kvinners Sanitetsforening,* a women's association working in the interest of public health and welfare, has been very active. This organization also granted financial aid, which was of considerable assistance. Under the leadership of its energetic chairman, *Mrs. Karen Asting,* this association assisted in the reporting of cases and their presentation for medical examination. Valuable assistance also was received from the *Norwegian Public Health Service* through *Dr. Fredrik Mellbye,* from the *County Medical Officer for Østfold, Dr. Harald Bjelke,* and from the local public health nurses.

Dr. Roald Rinvik, head of the Children's Department, Oslo City Hospital, Ullevål, read the manuscript and offered valuable criticisms.

The Norwegian Research Council for Science and the Humanities met the cost of translation and printing.

I should like to express my most grateful thanks to all the institutions and individuals whose assistance has made it possible to carry out this work.

Vækerøveien 171 B, Oslo, December 1956. *Bjarne Andersen.*

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CONTENTS

CHAPTER I

INTRODUCTION

Definition.

W. M. Phelps (1948) has defined cerebral palsy as "all those conditions in which interference with the control of the motor system (nervous and muscular system) arises as a result of lesions within the brain". This condition should not be confused with other types of palsy, such as 1) progressive lesions of the brain (e.g. tumors), 2) lesions or diseases of the spinal cord and brain stem (e.g. poliomyelitis), or 3) of the peripheral nerves (e.g. neuritis).

The designation *infantile* cerebral palsy means that the disease is present in the first few years of life, having occurred before, during or after birth. There is no set age limit with regard to the time of the disease's appearance.

Infantile cerebral palsy is not a single illness, but a syndrome. Perhaps it would be more accurate to say it is a number of conditions *consequent* to lesions of the brain. These conditions have widely varying symptoms, but for purely practical reasons they fit into a single group. The same etiological factors are found, generally speaking, and modern treatment of the various forms or types follow the same general rules as regards physiotherapy, occupational therapy, school education and vocational training.

It is obvious that a brain lesion will very seldom affect the motor centers selectively. Several other centers may be involved at the same time, so that the motor lesions will often be combined with other disorders, such as mental defects, epilepsy, visual and auditory disorders, and so forth.

The Development of Therapy for Cerebral Palsied Children.

W. J. Little (1862) was the first to describe the illness that came to be known as *Little's disease.* This was the form of cerebral palsy that is now known as *spasticity.* In the beginning, this condition usually was treated surgically by lengthening the sinews to offset the effects of contractures (e.g.

short heel-cord), severing muscles or nerves, or possibly performing osteotomy or arthrodesis in order to improve the child's ability to use the limbs.

It was about 1917—1920 that the medical treatment of this condition was begun in the United States by *Bronson Crothers*, a pediatrician, and *W. M. Phelps*, an orthopedic surgeon. The principles advocated by these men and followed since they undertook the treatment of cerebral palsy include co-operation among a number of therapists and doctors. There is "teamwork" in the true sense of the word, carried out by working-parties in which the physiotherapist works side by side with the nursery school teacher, occupational therapist and speech specialist. In school the children have a specially trained teacher. On the medical side, co-operation is expected among pediatric, neurologic and orthopedic specialists. The aim is to reduce the child's handicap as far as possible through intensive training that may take years, to find a suitable occupation for each child, and to help him to become an individual who is of use to the community and does not need public support.

In *England* this work was taken up between 1940 and 1945. In *Norway* it was taken up along modern lines in 1950, at the same time as the founding of a voluntary aid organization whose aim is to deal with the various problems arising from cerebral palsy (the Infantile Cerebral Palsy Association). Similar work was started in the other Scandinavian countries at about the same time.

Statement of Problem.

It is very important, when beginning work connected with a special social problem, to pose a number of questions early in the undertaking and, if possible, even in advance of the actual beginning. For many years cerebral palsied patients have been admitted to hospitals, thus providing case material that has been carefully examined and consequently is eminently suited to a study of the *clinical* situation. However, such cases are not so suitable for a study of sociomedical problems produced by such individuals in a section of the population. The group is too strictly selected, and there is little opportunity to include the less involved cases. The case material provided by a hospital does not give much indication of the relative incidence of the condition in the country as a whole. Norwegian law lays down clear rulings regarding the obligation to report the conditions with which we are concerned here. This requirement ought to make it easy to obtain a reliable impression of their frequency, but these rulings are ignored, as will be seen later.

The aim of this study is three-fold. First an enquiry was to be made into the *incidence* of cerebral palsy in Norway. In addition it has been considered important to examine the *distribution of the various types* of cerebral palsy in a collection of case material that includes the less involved cases. Further, an attempt was made to throw some light on the etiologies. Finally it was important to consider the situation with regard to *diseases or defects which accompany the condition* (mental, speech, visual, auditory), the arrangements made for *educating* these children, their scholastic potential and achievement, and the possibility of their being *trained for some occupation.* These enquiries provide the basis for demonstrating the *need* for various forms of treatment, homes for treatment, and so forth.

Second, an attempt was made to throw some light on the *financial aspects* of the problem, to find out what it means, financially speaking, for parents to have a child with cerebral palsy, and what it may cost the insurance services, state and loal authorities to provide financial assistance.

Third, with the foregoing information as a background, an outline is given of *preventive and other measures* that should be undertaken to give the children effective help and treatment. An attempt is made to estimate approximately what it will cost to give all the affected children the treatment they need.

CHAPTER II

INCIDENCE OF INFANTILE CEREBRAL PALSY

Enquiries in other countries.

The ideal method of discovering the incidence of a disease or condition among a section of the population is, of course, to examine every individual in the section. However, this is not practicable where a large section of the population is concerned, and a large section must be considered if the statistics are to give a true picture of the population as a whole.

In an enquiry into the incidence of cerebral palsy in *Schenectady County, N.Y., U.S.A.* (1949), the method was adopted of first obtaining reports from all hospitals, medical institutions and authorities, and doctors in the district of 137,488 inhabitants. All cases examined and treated were reported. Trained medical students then conducted a "house-to-house" enquiry, which covered 16.4 per cent of the population. Suspected cases were submitted for special examination. For every 10 cases reported in the first part of the enquiry, the second part, the "house-to-house" enquiry, yielded 7 additional cases. 5.9 cases of cerebral palsy per 1000 births were discovered. Enquiries in New Jersey and Maryland by *Phelps* (1941) yielded 4 cases per 1000 births.

In *Europe* there have been no enquiries conducted with such thoroughness as in America, and the results of European enquiries show considerably lower incidence. Examining *English* schoolchildren between 5 and 15, *Asher and Schonell* (1950) found 1 case per 1000 live births. *Scheel Thomsen* (1952), examining children up to 16 years of age in Fyn, found that the incidence in *Denmark* amounted to 1.5 cases per 1000 births. *Nilsonne* (1951) reported that in *Sweden* one child is born with cerebral palsy per 100,000 inhabitants per year. Remembering that the Swedish birthrate in 1950 was 16.5 per 1000 inhabitants per year, an estimated incidence of 0.6 cases per 1000 births can be made.

The Author's Enquiries.

In order to discover the incidence of infantile cerebral palsy in Norway and the problems of a sociomedical nature arising out of the condition

in this country, it was decided to investigate the situation in the county of Østfold. This county is relatively small in area (4,180 km^2), with a population of 185,419 (according to the 1950 census), 55,988 or 36 per cent of whom lived in towns (the figure for Norway as a whole was 30 per cent at that time).

Distances are not so great in this county that much difficulty is encountered in examining all the cases discovered.

Østfold county has a greater number of doctors than many of the northernmost counties. It is better supplied with hospitals and maternity homes than many other counties, and expectant mothers have a relatively short distance to travel for their confinement. More confinements take place in hospitals or maternity homes providing good treatment than in the northern counties.

These conditions should mean that the number of birth injuries resulting in cerebral palsy might be expected to be smaller than in many other counties. The figures obtained for this county probably will be below the average for the country as a whole. For this reason it should not be assumed that the figures for Østfold are representative of the country as a whole. An enquiry would have to be made in several counties to insure a more reliable report. However, the present enquiry should yield a certain amount of useful information with regard to the size and scope of the problem in Norway.

In order to discover as many cases as possible, the enquiry was conducted in the following way:

1. Reports were obtained from the district doctors and nurses as to the cases assumed to be cerebral palsy known to them in their districts.

2. After these reports had been obtained, one of the women's aid organizations (the Østfold branch of Norske Kvinners Sanitetsforening), together with the local district nurse with an intimate knowledge of local conditions, located suspected cases. By means of written information and talks accompanied by films, both nurses and voluntary helpers were instructed as to what conditions might be cerebral palsy and thus relevant to the survey.

3. Records were borrowed from the hospitals to which children from Østfold are usually admitted (Children's Department of the Norwegian State Hospital, Neurological Department of the State Hospital, the State Home for Mental Defectives—Emma Hjorts Home, Solbø, the Coastal Hospital at Stavern, the State Clinic for the Disabled—Sophies Minde).

Table 1.

Collection of material.

Reported by	Cases reported	Examination refused	Examined (by author)	Suffering from cerebral palsy	Percentage of c. p. among those examined
Medical officers	68	4	64	44	68.8 %
Voluntary organizations	54	7	47	21	44.7 %
Hospitals & institutions	12		5*	12	
Total	134	11	116	77	

*) 7 cases were not examined by the author, but the hospital records were consulted.

Only patients under the age of 21 have been examined, as this group is considered most receptive to treatment.

Table 1 shows the result of collecting the material. It will be seen that 77 cases of cerebral palsy were found. In addition, there were 11 other possible cases of cerebral palsy, but these refused to be examined. Of the 111 cases examined outside hospital, 65 proved to be cerebral palsy, i. e. 58.6 per cent of those examined. It may be estimated that examination of the other 11 cases would have yielded about the same percentage of actual cases. If it had been possible to examine these, an additional 7 cases thus would have been found, giving a *total of 84 cases of cerebral palsy under the age of 21 in the county of Østfold.* These figures must be regarded as minimal, as there will always be cases that are left out of any enquiry. Table 1 illustrates, further, the importance of obtaining the assistance of voluntary organization with a large number of interested members in work of this kind. 56 cases were found through medical officers and medical institutions, but in addition to these, the help of non-medical volunteers resulted in the discovery of a further 21 cases, i. e. 3.75 new cases per 10 cases reported. It is true that the number of actual cases in relation to cases reported was considerably lower in respect of the voluntary organizations (44.7 per cent) than of the medical officers (68.8 per cent), but nevertheless, this contribution to the enquiry must be regarded as valuable.

Distribution of cases in the county.

Table 2 and fig. 1 show how the cases were distributed over the county. As might be expected, most of the cases were found where the population is

most dense: in and near the towns. The ratio between town and country corresponds well to the distribution of the population.

The figures concern the 77 actual cases examined.

Table 2.

The geographical distribution of cases in the county of Østfold

Urban or rural district	Number of inhabitants (1950)	Number of cases of cerebral palsy
Aremark	1 724	1
Askim	8 609	1
Berg	7 618	3
Borge	6 452	1
Degernes	1 849	1
Eidsberg	6 142	4
Fredrikstad	14 326	8
Glemmen	13 958	8
Halden	9 939	3
Hobbøl	2 790	1
Hvaler	3 345	0
Idd	5 841	1
Kråkerøy	4 569	4
Moss	18 449	5
Mysen	2 525	2
Onsøy	8 953	1
Rakkestad	5 660	1
Rolvsøy	2 925	1
Rygge	4 609	8
Rødenes	1 395	0
Rømskog	648	0
Råde	3 429	2
Sarpsborg	13 234	7
Skiptvedt	2 626	1
Skjeberg	9 473	4

See pag. 16 too.

Urban or rural district	Number of inhabitants (1950)	Number of cases of cerebral palsy
Spydeberg	2 863	2
Torsnes	1 340	1
Trøgstad	4 170	0
Tune	10 299	4
Varteig	1 167	1
Våler	2 332	0
Øimark	2 120	0
County of Østfold	185 419	77
Towns	55 988	23
Country districts	129 431	54

Age distribution.

A close study of the distribution among age-groups (Table 3A) gives rise to a number of observations.

It is to be expected that the cases will be distributed fairly evenly, with approximately the same number of new cases per year in the same age-group. On account of deaths, it might be expected that a graph of cases distributed according to age would be highest in the first age-group, provided *all* patients were included. The higher the deathrate, the steeper the fall in the graph ought to be. The age distribution of the present material shows a majority of cases in the 5—9 age-group, and fewer in the 0—4 age-group. The reason for this is obvious: the diagnosis was made at a late stage, partly because the parents were late in discovering that there was something the matter with the child, and thus were late in getting medical advice. In addition, the reason is partly that we doctors are often late in recognizing the symptoms as cerebral palsy.

A glance at the figures for each individual year in the first five years of life (Table 3B) shows the same, that the diagnosis was made at a late stage: there is a distinct rise in the number of cases in relation to the rise in age.

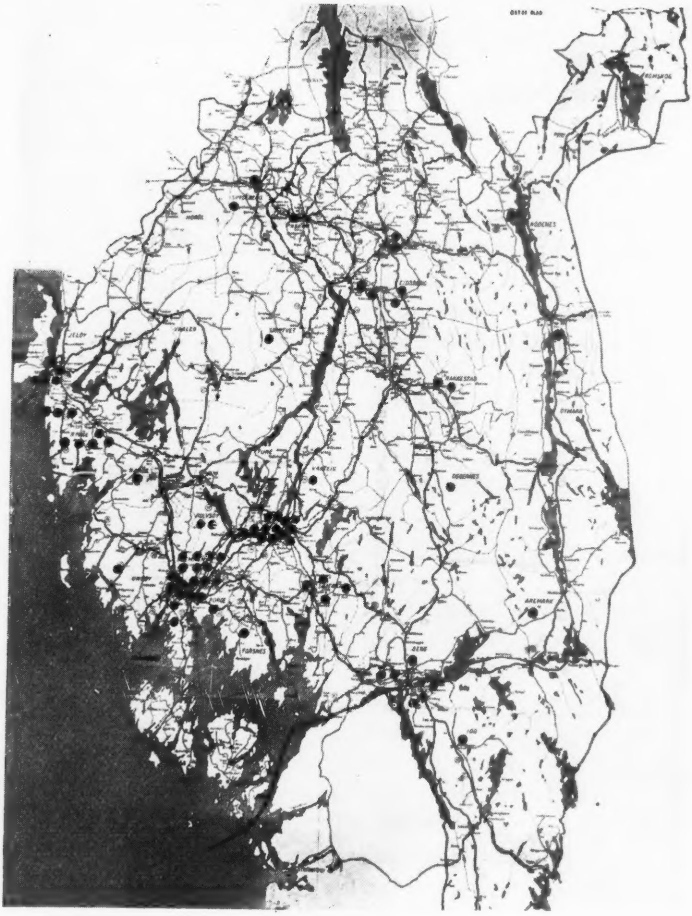


Fig. 1.
The geographical distribution of cases in the county of Østfold.

Table 3. A.
Distribution of material in age-groups.

Age:	All ages	0—4 years	5—9 years	10—14 years	15—19 years	20 years
Number of cases	77	26	33	9	8	1

2 Infantile cerebral palsy.

Table 3. B.

Distribution among single years in the first five years of life.

All cases	< 1 year	1 year	2 years	3 years	4 years
26	1	3	5	9	8

The incidence is considerably lower in the 10—14 age-group than in the 5—9 age-group, but it is impossible to give any definite reason for this. It is probably due partly to a death-rate being above the average, but also it must be partly due to the fact that a number of slight cases improve to such an extent that they are not included in a report of this kind. Some mental defectives with cerebral palsy may possibly have been sent away or even, in rare cases, "hidden away" by their parents.

The fact that the 5—9 age-group is the largest may be explained by the fact that it is at this age—when they begin school—that children come into increased contact with the outside world. Greater demands are made on them, and they are more likely to be reported if they are suspected to be suffering from cerebral palsy.

Examination of the incidence in other countries has shown age distribution similar to that in the present material.

In estimating the incidence of cerebral palsy, one ought to be able to base one's calculations on the age-group with the highest rate of incidence, i. e. the 5—9 age-group. In Østfold 33 cases were found in the 5-year period, which means an average of 6.6 cases per year. As this is among a population of 185,419, it corresponds to *3.6 new cases per year per 100,000 inhabitants.* In his enquiries in the U.S.A., *Phelps* (1941) found 7 cases per year per 100 000 inhabitants. *Perlstein* (1955) believes that there are many more slight cases than is usually assumed, and estimates the incidence of cerebral palsy at 10 cases per year per 100,000 inhabitants.

The birth-rate in Norway is 18.6 live births per year per 1000 inhabitants (18.6 is the average for the years 1951, 1952 and 1953, according to official Norwegian statistics). On the basis of an estimated 3.6 new cases of cerebral palsy per year per 100,000 inhabitants, this will give *1.9 cases of cerebral palsy per 1000 births in Norway.*

The enquiry in Østfold revealed a total of 77 cases of cerebral palsy. In addition to these, there are the 7 cases estimated among the 11 who did not wish to be examined, hence a total of 84 cases. These are in the age-group under 21, which comprises 30.8 per cent of the whole population of Norway. If it is assumed that the death-rate among adults suffering from cerebral palsy

is the same as among the rest of the population, there should be a total of 273 cases in Østfold, or *147 cases per 100,000 inhabitants.*

Basing calculations on the age-group with the highest incidence (5—9 years), and assuming an average lifetime of 65 years, one gets *234* cases per 100,000 inhabitants.

Certain reservations already have been made in respect of regarding the figures for Østfold as representative of Norway as a whole. If, however, they are regarded as being representative, the following results are obtained. According to official Norwegian statistics, 62,500 live births were registered in 1952. Assuming there to be 1.9 cases per 1000 births, *119 children with cerebral palsy should then be born in Norway per year.* We should have about 2,500 patients under the age of 21, and about 7,700 cases among the population as a whole (using the 5—9 age-group as a basis for these calculations).

The number of new cases per year (119) must be assumed to be less than the actual figure, because the number of cases in the first five-year period (0—4 years) should be higher than in the next (5—9 years) if all cases were included and deaths counted. The estimated figure for cases under 21 and for cases among the population as a whole does not, however, reckon with the abnormally high death-rate that must exist even after the age of 5—9, on account of reduced resistance to infection, and so forth, and probably is too high.

The most accurate estimate of the total number of cases there must be under 21, probably is to be obtained by calculating on the basis of the *total number* found in Østfold in this age-group, i. e. 84 cases. Thus there should be *approximately 1,500 cases under 21 in Norway.* This figure should be a conservative estimate, based on a county in which conditions are better than in most other counties in Norway.

For the purpose of comparison, Table 4 gives the results of enquiries into incidence of cerebral palsy in various countries. The number of cases per 1000 births is given first to provide a specific basis for comparison. Then the estimated number of cases in a section of the population comprising 100,000 inhabitants is listed. But there are several uncertain factors in this connection. For one thing, it has been assumed that the death-rate is the same among people suffering from cerebral palsy as among the rest of the population, but this is hardly the case. As has already been noted, probably there is a rather higher death-rate—on account of more frequent infection, poorer resistance, and so forth.

Table 4.

Incidence of cerebral palsy in various countries.

Country	No. of cases pr. 1000 births	No. of cases pr. 100 000 inhabitants
U.S.A.		
Phelps	4.0	390*)
Schenectady County	5.9	152
		591**)
England.		
Asher & Schonell	1.0	105***)
Denmark.		
Scheel Thomsen	1.5	135
		208**)
Sweden.		
Nilsonne	0.6	65**)
Norway.		
Author's investigation	1.9	147
		234**)

*) Average span of life regarded as 65 years.
**) Based on 5—9 age-group and an average span of life of 65 years.
***) Based on 16 births per 1000 inhabitants per year (official British statistics for 1950).

It will be seen from the above table that there is a noticeable difference between the estimated incidence in Europe and the U.S.A. This difference *may* exist in reality, but it also may be due to the way in which the material has been collected. The American enquiries reported here have been conducted by examining every individual within a certain section of the population. In general, the European enquiries are based on reports made by doctors and medical institutions which do not always include less serious cases. In the present enquiry that procedure has been modified in that assistance has been obtained not only from public medical authorities, but also from interested but untrained helpers. The result of using this system of case collecting is that the incidence has been found to be higher than in previous European enquiries, but it is still lower than found in the American enquiries.

Doctors' obligation to report cases.

Norwegian law requires doctors to report the presence of cerebral palsy in children, so that it should be a simple matter to investigate the incidence

of cerebral palsy. According to the Act of June 19, 1936, "any doctor who in the course of his duties observes disability or threatened disability in any patient under treatment or observation, is required to report the case within one month to the local health authority, using a special form and giving information as to the nature of the disability. The chairman of the health authority shall supervise persons receiving aid in accordance with the law in respect of disabled persons". (Quoted *Marthinsen, Koren & Strøm* 1955.)

In order to learn to what extent doctors comply with this regulation, the Østfold section of the register kept by the Central State Committee for the Care of the Disabled has been examined. The local health authorities are required to forward reported cases of disability to this register. It was found that only 10 of the 77 cases discovered during the enquiry appeared in the register. Two cases reported in the register have not been traced, either in reports from the public health officers or in reports from the voluntary organizations. Of the 77 cases, there were 71 who are in need of treatment or supervision, and who ought therefore to have been reported to the register. Thus there are noticeable shortcomings both as regards to reports from the practicing doctor to the health authority, and those from the health authority to the central register.

As has already been stated, it is the under 21 age-group that is the object of this enquiry. But it is also interesting to go through the central register with regard to cases of cerebral palsy over 21 years of age. In the case of Østfold, 39 patients were reported, usually rather more serious cases. Such cases seem to be more certain of being reported. For one thing, these patients belong to an age-group which, in accordance with the temporary Act of July 16, 1936, at present is entitled to financial assistance to the extent of kr. 1,440 per annum. They must be over 16 years of age and severely disabled by a congenital or acquired defect which interferes with the functioning of body parts used for movement or support (over 80 per cent invalidism) in order to be entitled to this assistance.

CHAPTER III

CLASSIFICATION ACCORDING TO TYPE

Infantile cerebral palsy, as stated by *Perlstein and Barnett* (1952), may be classified in various ways, each of which has both advantages and disadvantages:

1. According to the site of cerebral lesion.
2. According to symptomatology.
3. According to which extremities are involved (extent).
4. According to degree of lesion.
5. According to muscular tone.
6. According to causes.

The first and fifth type of classification are of minor importance in an enquiry in which the stress is on the sociomedical aspects of the condition. These will not be discussed.

Classification according to symptomatology:

Clinical classification according to symptomatology has an important bearing upon treatment. The number of patients available in an enquiry based on a single county is rather small for classification. On the other hand, it may be interesting to consider the distribution among case material of this kind, which includes less involved cases. Classification has followed the same principles as employed by *Phelps* (1949). *Perlstein* used a slightly different clinical classification from the one introduced earlier by Phelps (5 types: Spasticity, Athetosis, Ataxia, Rigidity, Tremor). Inasmuch as the latter method is the one used previously in similar enquiries, it will be adopted here. Patients are placed in the group to which their most conspicuous symptoms belong, and only cases showing marked symptoms of more than one type are described as being of mixed type. (Table 5.) It will be seen that the distribution in the Østfold material is in precise agreement

with *Pohl's* (1952) from the U.S.A. There is a striking divergence from the enquiries conducted by *Seyfarth* (1951) and *Salomonsen & Skatvedt* (1954). These investigators found mixed types in 17.5 per cent and 25.6 per cent of cases respectively, while other authors' figures vary between 1 per cent and 4.2 per cent. This difference may be explained to some extent by the fact that the authors who reported a higher incidence worked with case material having more serious lesions. Hence the higher incidence of mixed types. But it seems to this author that the main difference is to be found in the *method* of registration, in that they undertook a more detailed and precise neurological differentiation. This is certainly of great interest from a scientific point of view, but it is of less importance from a practical and therapeutic point of view.

Table 5.
Comparison of type distribution in various enquiries.

	Spasticity	Athetosis	Ataxia	Tremor	Rigidity	Mixed type
U. S. A.	%	%	%	%	%	%
Pohl, 144 cases	66	19	8	2	4	1
England Asher & Schonell, 349 cases	83	10	1	0,3		Flaccid. 0,6
Denmark Scheel Thomsen, 118 cases	77,1	9,3	6,8	0,9		4,2 (others 1,7 %)
Norway						
Seyfarth, 63 cases	58,5	17,5	6,5			17,5
Salomonsen & Skatvedt 320 cases	55,3	14,1	5			25,6
Andersen, Bj., 186 cases	63,5	17,2	10,2	1,1	6,5	1,6
Østfold material 77 cases	65	19,5	11,7	1,3	2,6	

Classification according to which extremities are involved (extent):
Classification according to degree of lesion:

Classification according to which extremities are involved must be seen in relation to the degree of injury, for generally speaking, the more the extremities involved, the more serious the case. This does not apply to athetosis which usually affects the entire motor system, nor to ataxia, which primarily affects co-ordination. It is primarily in the case of *spasticity* that classification according to extent is of importance. The 50 cases of spasticity found in Østfold were distributed thus:

Monoplegia	3 cases	6 %
Hemiplegia (4 right, 11 left)	15 "	30 %
Paraplegia	19 "	38 %
Triplegia	1 "	2 %
Quadriplegia	12 "	24 %
Total no. of spastics	50 cases	100 %

It is much more important in estimating what measures will be necessary, when planning a rational program of treatment for these patients, to classify the cases according to their degree of severity. Cases are classified as *mild, moderate* and *severe*. The system used will be seen in Table 6 (*The Study of Cerebral Palsy in Connecticut*, 1951), in which attention is paid both to the number of extremities affected and the degree of handicap in these extremities.

Table 6.

Classification as mild, moderate and severe cases.

Number of extremities affected	Functional capacity		
	Grade A	Grade B	Grade C
1	Mild	Mild	Moderate
2	Mild	Moderate	Severe
3	Moderate	Moderate	Severe
4	Moderate	Severe	Severe

Grade A: Practically no loss of function.
Grade B: Moderate loss of function.
Grade C: Severe loss of function.

Table 7.

Distribution of cases according to age and degree of severity.

Degree	Age (years) 0—4	5—9	10—14	15—19	20	Total
	%	%	%	%		%
Mild cases	8 (31)	13 (40)	3 (33)	1 (12)		25 (33)
Moderate cases ..	11 (42)	14(42,5)	4 (45)	4 (50)		33 (43)
Severe cases	7 (27)	6 (18)	2 (22)	3 (38)		18 (24)
Not known					1	1
Total	26 (100)	33 (100)	9 (100)	8 (100)	1	77 (100)

In Table 7 the cases are divided into age-groups and according to their degree of severity. However, grading cannot be entirely accurate during the first five-year period, since even normal children have very few motor accomplishments during the first year or two of life. (The above grading is based on Gesell and Amatruda's "Preliminary Behaviour Inventory" [1951]).

Usually it is estimated *(Perlstein* 1955) that 25 per cent of all cases are slight cases. The group comprising medium cases is the largest, containing about half of all cases. The remaining 25 per cent are severe cases. The Østfold results correspond well with this distribution. In the 5—9 age-group there is a rather higher incidence of slight cases which should indicate that the enquiry has succeeded in tracing and including children with slight invaluement.

CHAPTER IV

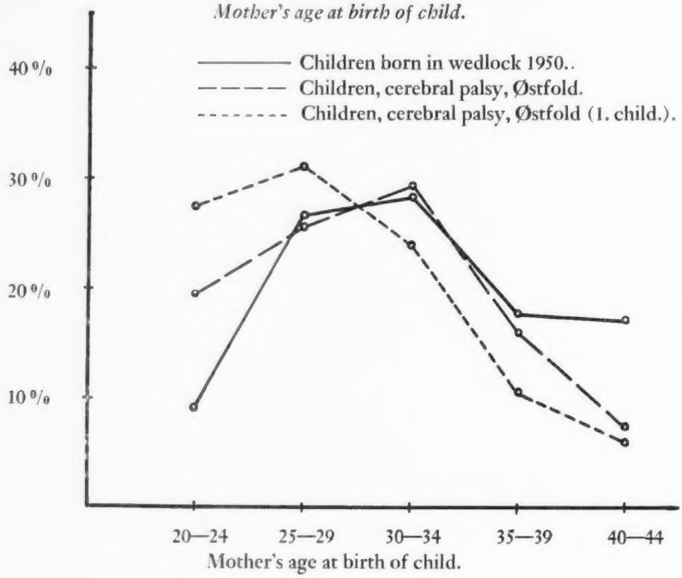
CAUSES OF CEREBRAL PALSY

In collecting the Østfold material, an attempt was made to obtain full and accurate information regarding the mother's health during pregnancy, the obstetrical history, and a record of the child's first few years of life. This was done to obtain information regarding factors that might bring light to bear on the causes of cerebral palsy in the cases used in this study. The number of patients it is possible to examine in an enquiry into conditions in a single county is somewhat too small to provide a basis for any thorough analysis of the causes, but may be of some interest nevertheless.

Perlstein (1949) gave an enumeration of the etiological factors that may be involved, and his classification has been used in this report.

Fig 2.

Mother's age at birth of child.



The 77 cases that have been carefully examined in the county of Østfold show the following *sex* distribution: 45 boys and 32 girls, a definite preponderance of boys. The distribution among town and country districts shows that incidence is the same in town and country, taking into account the relative population figures (see Table 2). 52 of the children were born at maternity homes or hospitals, 10 at home, and in 15 cases no details of the place of birth were available.

Figure 2 shows the *age distribution of the mothers.* The corresponding age distribution of the mothers of all children born in wedlock in Norway in 1950 is also shown for the purpose of comparison. It will be seen from the graph that there is a preponderance of *younger* mothers (in the 20—24 age-group). It is usually assumed that the first child of an older mother is more susceptible to cerebral palsy. Therefore graph showing the age distribution of mothers of first children has been added to Fig. 2. There is no preponderance of older women in relation to the normal population in this group either. On the contrary, the preponderance of younger age-groups seems to be even more pronounced.

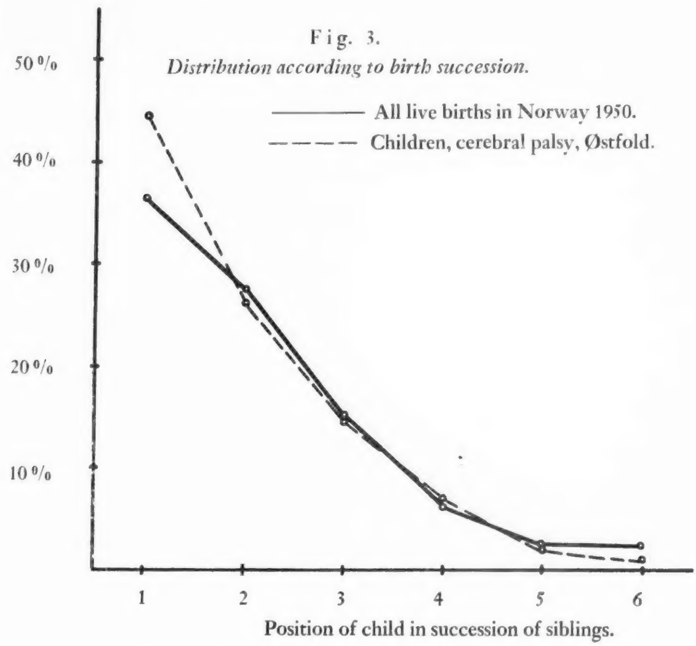


Fig. 3.
Distribution according to birth succession.

Figure 3 shows the distribution in relation to the *child's position in th succession of siblings.* A corresponding graph in respect of all live births i Norway in 1950 is included for the purpose of comparison. It will be see that a first child is more susceptible to injury than later children.

Information regarding the mother's health during pregnancy was availabl in 61 cases. Abnormal conditions were present in the following cases:

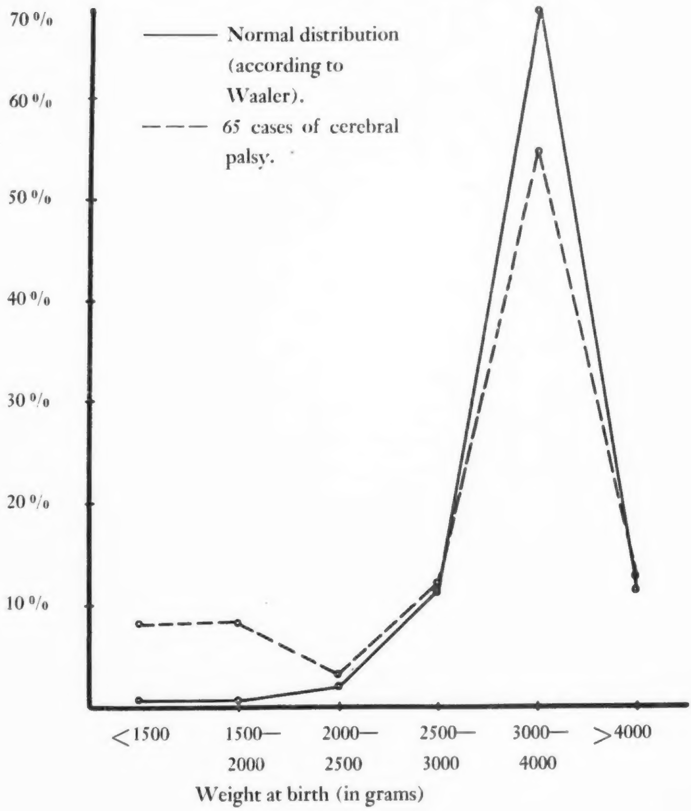
Toxemia	4	cases
Hypertension	1	"
Haemorrhage during pregnancy	1	"
Fainting " "	1	"
Influenza during the first quarter	1	"
Avitaminosis (?)	1	"

The remaining 52 had a normal pregnancy. Possibly congenital, perhap hereditary, factors were present in 3 cases in which the children had othe concurrent deformities. Avitaminosis probably occurred in one case, as re- ported. The patient was a boy with spastic quadriplegia. The birth had bee entirely normal, and the only pathological factor discovered in an intervie with the mother was the fact that her diet had been extremely deficien during pregnancy and that she had suffered from night blindness during thi period. In this connection, attention is drawn to Warkany's experiments o rats, showing that the offspring of rats kept on a diet deficient in riboflavi frequently had multiple defects (quoted by Perlstein, 1949).

The duration of pregnancy seemed to have some influence on the occurr- ence of cerebral palsy. Both prematurity and hypermaturity are known t be predisposing factors. Exact data as to the duration of pregnancy are no available, however, and the weight at birth is the best indication, in spite o the fact that the weight at birth and the duration of pregnancy do not alway follow a proportional pattern. The length of the infant at birth is seldom remembered by the mother. In the Østfold material the weight at birth wa given in 65 cases. Figure 4 contains a graph showing the distribution of th cases according to weight at birth. A graph in respect of normal subject i added for the purpose of comparison (*Waaler*, 1933). It will be seen from these graphs that cerebral palsy occurs more frequently among childre with a low birth-weight (prematures), but not among children with a high birth-weight in this survey.

Fig. 4.

Distribution of cases according to weight at birth.



Regarding the obstetrical history, information as to the *duration of labour* was available in 63 cases. In 37 cases (59 per cent) labour was of normal duration, in 10 cases (16 per cent) labour was precipitate, and in 16 cases (25 per cent) it was prolonged. The *position of the foetus* was known in 53 cases. The position at birth was normal in 41 cases (78 per cent). There was breech delivery in 6 cases (11 per cent) as against 3.6 per cent of all other deliveries in 1950. Transverse, forehead, brow and face presentations occurred in 6 cases (11 per cent). A *Cæsarean section* was performed in one case. *Forceps* were employed in 13 cases, or 20 per cent as against 0.9

per cent of all other deliveries in 1950. A *general anæsthetic* was administered in 16 cases (25 per cent). Ether was used in nearly every case.

Information was available regarding the *condition of the child immediately after birth* in 66 cases:

Normal	29	cases
Weak or blue (resuscitation necessary in 12 cases)	34	"
Incubator	1	"
Oxygen treatment	2	"

Erythroblastosis may have been present in one case. The patient suffered from jaundice during the first day of life. On examination, the child was found to be a deaf athetoid, with restriction of eye movement in a vertical direction.

Information regarding *post-natal brain injuries* was available in 7 cases:

Meningitis	1
Encephalitis	2
Trauma capitis	2
Malignant gastro-enteritis with toxæmia and brain-injury	2

Any attempt to sum up the various causes usually will have to be related to birth. As will be seen from Table 8, the causes are classified as pre-natal, natal and post-natal, according to when the injury seems to have been inflicted. Approximately 30 per cent of cases seem to have been caused prenatally, 60 per cent natally and 10 per cent post-natally. Any such division into categories is bound to be a matter of judgment, since often it is impossible to state the actual cause. In the case of a breech birth, for example, the position of the foetus may be abnormal because of defect movements on the part of the foetus, due in turn to an injury or defect in the neuromotor system of the foetus. The brain injury already will be present, and is the *cause* of the breech birth instead of having arisen later *on account of* the breech delivery. Sometimes the case history will reveal several factors that may be the cause of the condition.

The distribution according to suspected causes in the Østfold material corresponds quite well to the usual distribution, in that most of the cases in which it has been impossible to state a definite cause are presumably due to pre-natal factors.

Table 8.

Causes of cerebral palsy in the Østfold material.

Pre-natal causes (hereditary and arising during pregnancy)	12	cases	16.5 %
Natal causes	48	"	66 %
Post-natal causes	7	"	9.5 %
No traceable causes	6	"	8 %
Total	73	cases	100 %
Insufficient information	4	"	
	77	cases	

CHAPTER V

DISEASES AND DEFECTS EVIDENT IN CONJUNCTION WITH INFANTILE CEREBRAL PALSY

As has already been stated, brain injuries giving rise to cerebral palsy do n affect the centers of the brain selectively. The condition is often complicat by other injuries which have to be considered when deciding whether patient is treatable, when planning a program of treatment for him, or wh giving advice regarding his future occupation.

Mental condition.

Active co-operation on the part of the patient is essential in the treatme of cerebral palsy. The patient must have sufficient intelligence to be ab to co-operate if the treatment program is to be effective and if there is to carry-over of training routines.

In the case of healthy individuals, their intelligence can be estimated wh their intelligence quotient. (I.Q.) is established. When testing children, it necessary that they are able to express their responses by means of defin signals, speech, and so forth. For children suffering from cerebral palsy th often is impossible. News tests have been devised with such children mind but success has been limited so far. There is some value in establishi the I.Q. of cerebral palsy patients, but it is much more important, as stated *Denhoff* (1950), to study the child's behaviour, reactions, and contact wi the person making the examination. In the last analysis, the most importa thing is to observe what progress the child makes in the course of treatme and whether he seems to be deriving any benefit from it. Phelps attach great importance to such progress as a basis for further treatment rath than as a test of intelligence.

Opinions have changed from time to time on the subject of the intelligen in cases of cerebral palsy. Little, for example, thought most of these childr were mentally defective. When the work of treating the condition w started in the U.S.A., it was maintained that most of the children we

normal or nearly normal in intelligence, but that they were unable to express their intelligence in the normal way. In recent years there seems to have been some reversion to the former opinion, as indicated by the enquiries of *Asher & Schonell* (1950), *Miller & Rosenfeld* (1952) and *Hohman* (1952) (Table 9).

Table 9.

Grouping according to I.Q. of cerebral palsy patients and normal children.

	Intelligence quotient				
	< 70	70—89	90—110	110—129	> 130
Normal children (Hohman)	% 3	% 22	% 52	% 22	% 1
Children with cerebral palsy. Asher & Schonell (354 cases)	45	27	20	3,4	0,6 (4 % not tested)
Miller & Rosenfeld (330 cases)	50	22,5	23	4,5	
Hohman (462 cases) .... (The figures are approximate, read from author's graph)	60	25	12	3	

The enquiries conducted by these authors seem to indicate that the percentage of cerebral palsied patients of normal intelligence is considerably lower than among healthy children.

When the Østfold enquiry was carried out, it was impossible in most cases to do a thorough and long-term observation of the patients with a view to establishing their levels of intelligence. Therefore, the I.Q. was not stated. A rough evalution of mental development was undertaken, however, on the basis of the contact achieved with the child, and the child's behaviour during the examination. On this basis the children were classified as normal, retarded, and mentally defective. Rather more than half were assumed to be of normal intelligence, and a little less than half were retarded or mentally defective (Table 10). *Phelps* estimates the incidence of oligophreny at about 1/3 of

the cases. In the *Connecticut* enquiry (1951) it was found that 45.8 per cent were of normal intelligence, 21.4 per cent were retarded, and 30.5 per cent were mentally defective.

Table 10.

Distribution according to mental development.

Intelligence level:	Number of cases
Normal	46 (60 %)
Mentally retarded	16 (21 %)
Mentally defective	15 (19 %)
Total	77 (100 %)

The various enquiries into the intelligence level of children with cerebral palsy seem to indicate that about half of all cases may be supposed to be oligophrenic (mentally retarded or defective).

Speech defects.

Speech ability is often impaired by cerebral palsy. *Perlstein & Shere* (1946) say that 75 per cent of cases have speech defects. Between 50 per cent and 75 per cent of these are reported to benefit from speech therapy.

Table 11.

Speech ability in 48 cerebral-palsied children over 3 years of age.

(Excluding mental defectives.)

	Number of cases:
Speechless	4
Unintelligible	2
Intelligible, but not normal speech	21
Normal speech	21
Total	48

Table 11 shows the speech ability of the children in this study. Neither mental defectives nor children under the age of three are included. As will be seen from the table, more than half (57 per cent) had speech defects.

Vision disorders.

Guibor (1955) found vision disorders in 75 per cent of the cases in a group of 142 children with cerebral palsy. The disorders found were strabismus, conjugate deviations, nystagmus. Amblyopia often accompanies these defects. This precludes binocular sight (with depth perception), which leads to difficulties of co-ordination, walking and so forth. Vision disorders impose a complication on the cerebral palsy condition which makes it more difficult to treat.

In Østfold there was disturbed eye function in 17 cases (22 per cent):

Blind	1	case
Reduced sight (without strabismus)	3	"
Strabismus	10	"
Nystagmus	2	"
Nystagmus and strabismus	1	"
Total	17	cases

Auditory disorders.

Deafness was found in only one case, the patient with rhesus-athetosis. Hearing was normal in all other cases, according to the information provided by the parents and the author's examination.

Epilepsy.

Epilepsy often occurs among these patients. *Perlstein* (1955) finds real convulsions in at least 50 per cent of all spastics and in 10 per cent of athetosis cases. Pathological electroencephalograms indicate epilepsy in a number of patients, without there ever having been a seizure *(Perlstein, Gibbs & Gibbs,* 1946). There is a relationship between cerebral palsy and epilepsy in that physical treatment not infrequently aggravates epilepsy or reveals latent epilepsy. Experience shows that the treatment of epilepsy in patients with cerebral palsy is often more difficult than in other epileptics. Before treatment for cerebral palsy is begun, seizures must be kept under control by means of drugs, especially if the patient is subject to frequent seizures.

In the Østfold material convulsions occurred in the case history of 23 out of 68 cases (a third of the cases). No information was available in 9 cases.

CHAPTER VI

PROBLEMS CONNECTED WITH TREATMENT

As was stated in an earlier chapter, treatment for infantile cerebral palsy is not entirely new. For many years patients have received surgical treatment when necessary, and many cases have been treated by physiotherapy for varying lengths of time. What is new is that an attempt is now made to give them a number of *different* forms of treatment over a fairly long period, the object being to reduce their disability as far as possible. These forms of treatment consist of physiotherapy, play therapy or occupational therapy, speech training, various forms of orthopedic treatment, medical treatment, special schooling and occupational training. It is obvious that such comprehensive treatment will cost a great deal of money. It would be of great advantage if patients who would be certain to derive benefit from the treatment and to make progress functionally could be selected *in advance*. What happens in actual practice is that it is possible to pick out at once a group which is suitable for treatment. Another group is apt to be included which is unsuitable, either on account of oligophreny or such pronounced handicap that treatment would be useless. But between these two extremes there will be a fairly large number of patients who have to be given a trial period to see whether they make any progress. The group that is finally rejected as unsuitable should not be refused immediately and deprived of any form of treatment. A certain amount can be done for these patients too. For instance, it is sometimes possible to teach a mentally defective child with cerebral palsy to walk. This accomplishment makes looking after the child much easier. The Ministry for Social Affairs in Norway makes allowance for this in *Parliamentary Report no. 71* (1952) in respect to the national plan for the care of mental defectives, suggesting special homes for mental defectives who are deaf, blind, crippled or suffering from speech disorders.

In the group for whom treatment is tried for a time to see what can be done, there will be a number of cases whose treatment will have to be terminated when it is found to be of no avail. This leads to one of the

problems to be solved: how *long* should treatment be continued in each individual case?

The problems encountered in connection with the treatment of cerebral palsy can be summarized in the following questions:

1. How many of the patients need or ought to have treatment?
2. What forms of treatment may be used?
3. How long should the patients be treated?
4. Should treatment be handled on an in- or out-patient basis?
5. What demand is there for special schooling and occupational training?

The help we can give these children is still in its early stages, and as yet it is impossible to give an exact answer to several of these questions. A large

Table 12.

Patients' need for the various forms of treatment.

Age (years)	0—4	5—9	10—14	15—19	20	Total
Number	26	33	9	8	1	77
Needing physiotherapy	15	23	9	4		48
Receiving "	3	8		1		12
Needing play or vocational therapy	11	12	3			26
Receiving "		4				4
Needing speech training	7	13	5	2		27
Receiving speech training			3			3
Needing braces for correction or prevention of faulty positions	9	9	2			20
Provided with braces	1	1				2
Needing other aids (special chair, table, cycle)		9	3			12
Provided with such aids		2	1			3

number of patients will have to be treated for several more years before reliable answers can be given.

Table 12 is an attempt to give a partial answer to questions 1 and 2. This table is based on an estimate of every individual case made in the course of the enquiry. At that time very little was being done for these children in the county of Østfold, as can be seen from the table. It also shows how many receive the treatment they are believed to need. Considering the various forms of treatment, it will be seen that treatment has been given to between 10 per cent and 25 per cent of cases needing it.

Question 3 is difficult to answer until more experience has been gained. Generally speaking, it may be said that treatment should be continued as long as the patient is making progress, and as long as he is growing. In slight cases, treatment will become superfluous after a time, but they must be given periodic check-ups. In moderate and severe cases, treatment will be necessary for a number of years.

Out-patient treatment—In-patient treatment.

There are a number of factors influencing the decision to place a child in a residential center. Generally, if at all possible, *all* children should remain in their natural surroundings—the home. Thus, if there is the slightest possibility of managing by out-patient treatment, the patient ought to be allowed to stay at home. The first factor to be taken into account in deciding whether the patient can or should be treated as an out- or in-patient, is, of course, the *degree of severity of the case*. The most severe cases and those in need of several forms of treatment have to be admitted to residential programs. In Norway, *geographical* considerations play an important part in this matter. Distances do not need to be very great nor means of communication particularly poor before it is found that taking a child regularly for treatment involves too much time. In addition, *social* conditions and the attitude of the family also mean a great deal. Some parents make a special point of helping their disabled child and are willing to make any sacrifice,—others are indifferent. It is usually the mother who is in charge of the child's treatment at home, and it is she who sees to getting the child back and forth for treatment. A large proportion of the mother's time can be spent on this, and if there are several children in the family, the mother will not have time to look after the others properly with resultant harmful psychological consequences.

Table 13.

Need for out-patient treatment or residence in an institution.

Age (years)	0—4	5—9	10—14	15—19	20	Total
Number	26	33	9	8	1	77
Treatment superfluous	2	4				6
May be treated as out-patient	8	15	6	1		30
In need of treatment in hospital or other intitution	13	3	1	5		22
In other hospital or institution		1		3		4
Home for mental defectives may be indicated	2	9	1	2	1	15
In home for mental defectives	2	3		1	1	7
In need of nursing home	1	2	1			4

Table 13 shows the need for the various forms of in-patient treatment (center for treatment, homes for mental defectives, nursing homes) and for out-patient treatment. The cases were judged entirely according to their medical aspects, without regard to place of residence or size of family. An analysis of this nature only shows the need at the time of the enquiry. If a complete program for the treatment of all cases were to be set up, the need would be relatively great in all fields at the beginning. Even taking into account a steady stream of new cases, it will become easier to pick out those which are in need of treatment as more experience is gained. Treatment can be started at an early stage. This is to be regarded as an advantage, and it will be easier to decide when to stop treatment. All these factors will help to reduce the extent of treatment facilities which will be needed eventually.

CHAPTER VII

SCHOOLING AND TRAINING

In Norway disabled children—including children with cerebral palsy—between the ages of 7 and 18 are entitled to schooling in accordance with the primary school provision. If ordinary schooling is impossible, the Central Committee for the Care of the Disabled can rule that these children shall be admitted to special schools or given schooling at home. The costs are covered in accordance with the regulations regarding the treatment of the disabled. The costs are paid by the local authority, which in turn can claim whole or partial reimbursement from the person responsible for the child's maintenance. It is the local health authority which decides whether the latter is financially able to meet the cost. *(Marthinsen, Koren, Strøm,* 1955).

An enquiry among the patients' parents and teachers was undertaken in Østfold in the autumn of 1955 to find out what arrangements had been made regarding the schooling and training of all patients then of school age or older, a total of 46 cases. Of these, there were 30 who were attending or had attended primary school. Table 14 shows how these children got along at school. The statement describing the child's progress was obtained from the teacher and parent or guardian collectively.

It will be seen from Table 14 that fewer than a fourth do *very well* at school, rather more do *well*, and practically half do *less well* than the average. The table also shows how the children manage at school in relation to the severity of the case: The more severe the case, the greater the difficulty in keeping up. Of the 16 children who did not attend primary school, 3 were at special schools, 5 in homes for mental defectives, and 8 at home on account of oligophreny (5) or the severity of their cerebral palsy condition (3).

Transportation to and from school was the same in most cases as for the ordinary pupils (bus, bicycle or tricycle, on foot). Special transportation was used in only 2 cases. One was driven in the father's car each day; the other was taken by taxi.

Table 14.

Education of children with cerebral palsy in the county of Østfold

	Manage			
	Very well	Well	Not so well	Total
At ordinary primary school:				
Girls	4	5	3	12
Boys	3	5	10	18
Total	7	10	13	30
In relation to degree of severity:				
Mild	5	1	4	10
Moderate	2	8	7	17
Severe	0	1	2	3
Total	7	10	13	30
At other schools:				
School for the disabled				2
School for the blind				1
At homes for mental defectives				5
At home without schooling:				
Mentally defective and retarded				5
Severe cases of cerebral palsy				3

Home tutoring by a teacher was noted in two cases, both taking the form of extra instruction in addition to ordinary schooling. One child had one hour of extra instruction a week, and the other 6 hours. In both cases, the cost was covered by the local authority. In the second case this tutoring cost the local authority kr. 1000 in 1954 (approximately $ 140.00).

Training.

Occupational training could be considered in 7 cases:
1 boy (19) was learning shoemaking (at Sophies Minde).
1 boy (18) was learning how to do radio repairs.

1 boy (15) wanted to be a mechanic. There were training facilities in his home district.

1 girl (16) wanted to train for light office work. There were training facilities in her home district.

1 girl (19) wanted to learn weaving and other handicrafts, but there were no training facilities in her home district.

2 girls (19 and 16) had not made any choice of occupation.

Most patients with cerebral palsy in Østfold who are educable have access to primary education. However, as a matter of consideration for the other school-children and for the benefit of the child himself, it is better for those who because of severe handicap are unable to keep up at an ordinary school to be transferred to a special school. This type of child usually will have a greater motor handicap than the children with cerebral palsy who do well at school. He will have greater need for several forms of treatment simultaneously (physiotherapy, speech training and so forth) and thus should be in a place providing full treatment and schooling.

An estimate of the educational needs of individual cases shows the following figures:

6 are above school age.
10 ought to continue at an ordinary school.
9 are thought to be suitable for a special school.
5 ought to try a special school for a time.

The latter group—children who ought to try a special school for a time—consists partly of cases who ought to begin their education at a special school, but who should be transferred to an ordinary school as soon as they are ready for it. This category also contains cases who may derive no benefit from schooling, but who should be tried for a time in order to see whether it will be of any benefit.

Training could be considered in 7 cases. Arrangements had been made for 4 of these, while the other three needed vocational guidance and help in training. This problem does not seem to be great enough to be taken up locally in a single county, but should be handled in the country as a whole or in large sections of the country. It would then come in the same category as work for the benefit of other types of persons who are restricted in their choice of occupation.

CHAPTER VIII

FINANCIAL ASPECTS OF CEREBRAL PALSY IN ØSTFOLD

In order to obtain an accurate survey of the actual cost of cerebral palsy services to the various organizations and persons involved (state and local authorities, insurance companies, parents or guardians), one would have to get each of them to keep separate accounts for a specified length of time. Not all of them would welcome the extra work involved, and it would take some time to obtain replies. The method employed in collecting the present material, therefore, was to ask the various organizations and individuals selected questions in 1955 with regard to their expenses in 1954.

Replies were received from the treasurers of all the local authorities concerned, and several of them gave further information from the health authorities. Replies also were received from all insurance companies. Their accounts usually are not kept in such a way that it is possible to obtain information regarding expenses incurred through a certain illness. In the case of small insurance companies, where it is likely that individual cases are known, the information obtained presumably will be correct. The situation is not so simple in the case of the larger organizations, even though the name of the parent or guardian was given in some cases. Membership in an insurance company is listed according to place of work, not place of residence. However, the information supplied by the insurance companies regarding patients who have received treatment tallies well with the information the parents gave with regard to treatment (Table 12). Hence, it may be assumed that the main expenses have been reported.

It should be remembered that the information given by parents referred to the previous year and therefore may be subject to some inaccuracies.

Municipal and state expenses in 1954.

Disablement relief is granted in accordance with the Act of July 16, 1936, to disabled persons over the age of 16 suffering from over 80 per cent in-

validism, to the extent of kr. 1440 (approximately $ 205.00). (See p. 21.) Part of this is paid by the local authority and part by the state. This relief was granted to one patient under the age of 21 in Østfold.

Municipal disablement relief was granted in two cases to the extent of a total of kr. 3,480 (approximately $ 494.00). In one case the local authority had granted kr. 91.75 (approximately $ 13.00) for the purchase of braces.

On application, the parent or guardian of a disabled child may be placed *in a lower class* for the purpose of income tax assessment, provided the expenses incurred on account of the child's disablement have been great enough to warrant this. There were 58 answers to the question whether the parent or guardian had obtained this concession (12 affirmative answers, 46 negative). (New rulings have been in force since 1956, see p. 57.)

A total of 7 children who were mentally defective as well as suffering from cerebral palsy had been admitted to homes for mental defectives. The cost was met by the state as is usual in the case of mental defectives (the cost is guaranteed by the state, but reimbursement by the parent or guardian may be claimed if his financial circumstances allow). The state may claim reimbursement of 6/10 of the cost from urban district councils, or from county councils in the case of rural districts.

Insurance company expenses in 1954.

Insurance companies are obliged to cover the expenses incurred in treating cerebral palsy in the same way as for other illnesses. In the case of physiotherapy, the entire cost is borne by the insurance organisation. The cost of periods in hospital or in a nursing home is now covered by the insurance company without a time limit. The expenses incurred by insurance companies in Østfold in 1954 for patients suffering from cerebral palsy are shown in Table 15. The amounts are stated on the basis of the insurance companies' reports, but the reservations previously mentioned with regard to the accuracy of the figures should be borne in mind.

Table 15.
Insurance companies' expenses in 1954
for the treatment of patients with cerebral palsy (Østfold).

Doctors' fees	kr.	1 143.8
Physiotherapy	"	4 110.7
Hospitals, nursing homes	"	16 853.7

Grants for braces, special chairs, tables etc.	kr.	930.57
Travelling expenses connected with examination, treatment, admission to hospital and so forth	"	4 095.00
Insurance companies' total expenses	kr.	27 133.87

Parents' expenses.

Table 16.

Parents' expenses in 1954 for children suffering from cerebral palsy (58 cases).

Doctors' fees	kr.	417.00
Physiotherapy	"	252.00
Hospital	"	72.50
Special equipment (braces, chair, table, cycle)	"	3 766.50
Travelling expenses for examination or treatment	"	2 229.50
Travelling expenses for parents visiting children in hospital or nursing home	"	1 234.00
Other expenses (extra bedding, clothing and so forth) (Amount not stated in 2 cases)	"	2 098.00
Extra paid help on account of child	"	9 700.00
Income forfeited on account of child (85 working days altogether)	"	1 838.00
Total expenses for parents	kr.	21 607.50

In this enquiry into parents' expenses, the parents of 64 children were contacted. Cases too slight for treatment (6) and children in homes for mental defectives (7 cases) were omitted. Replies were received from 58 in all, i. e. 90 per cent.

The total expenses incurred by state, municipalities, insurance companies and parents amounted to about kr. 50,000 (approximately $ 7,143), according to these enquiries. The expenses thus appear to be very modest, but on the other hand this amount must be considered in relation to the member of those who have *received* treatment as against those *in need of* treatment. If Tables 12 and 13 are examined, it will be seen that only between 10 and 25 per cent of the patients have received the forms of treatment they need or

treatment in hospital or nursing home if needed. If it is estimated that about 20 per cent have received the treatment needed, it would have cost about kr. 250,000 (approximately $ 36,000) to give *all* cases in a single county full treatment. Of course, an estimate of this kind cannot be anything but a rough guess, but it gives some idea of the amount of money needed. It may quite rightly be maintained that it is incorrect to estimate the parents' expenses as constituting 20 per cent of what they would have been if full treatment had been given, especially for items such as extra paid help, the cost of extra bedding and so forth. On the other hand, the sum was arrived at without all cases being included.

CHAPTER IX

THE CHILD WITH CEREBRAL PALSY AND HIS RELATION TO THE FAMILY

A complete enquiry into the effects on a family of having a child with cerebral palsy requires that a number of problems be considered. The investigator must have specialized training and insight. This is particularly true when dealing with the psychological changes that take place in the child—and in the other members of the family.

Anyone who has had experience with these children is familiar with the variety of psychological reactions encountered in the patient and in the rest of the family. There are parents who will do anything to provide the child with all the treatment he needs. On the other hand, there are parents who give up so easily that about all they do is to reproach society for doing so little. A third type is seen in the over-protective parents who are so afraid of anything happening to the child that they dare not let him try his strength, and so are responsible for his retarded development. Other parents are ashamed of their child and try to keep him hidden away. Whatever is the feeling of the parents, the reaction of brothers and sisters usually will be influenced by the parents' attitude.

The child's attitude also will be influenced by the parents. Some patients are self-pitying, some demanding, and others have given up completely. Yet, there are also active children who go on working and are delighted when they make progress.

The *basic* ingredient for a better, more positive attitude on the part of the various members of the familiy is, of course, there being a *possibility* of progress and improvement by the cerebral palsied child. The fact that something is *happening* to the child, that the parents can *see* some progress, will tend to give them an optimistic, positive attitude that is a help to the child and of great psychological importance to the whole family.

In the previous chapter, the financial situation as a whole was explained. Table 17 shows the incomes of *individual parents or guardians*. This information was available in 54 cases, and for the purpose of comparison the

distribution of all persons paying income tax in Norway was given according to income group at tax assessment 1952/53 (Statistical Year Book of Norway 1954). The table shows that most of the parents or guardians have an income of between kr. 8,000 and kr. 11,900 p.a. (52 per cent). (Approximately $ 1,142.00 and $ 1,700.)

Table 17.

Patients' parents or guardians distributed according to income.

Income group	All Norwegian taxpayers 1952/53	Parents of children with c.p. 1954
kr.		
0– 2 900		4 cases (7 %)
3 000– 3 900	9 %	1 " (2 %)
4 000– 5 900	20,5 %	3 " (6 %)
6 000– 7 900	24 %	4 " (7 %)
8 000– 9 900	21 %	9 " (17 %)
10 000–11 900	11,3 %	19 " (35 %)
12 000–13 900	5,6 %	5 " (9 %)
14 000–15 900	2,5 %	5 " (9 %)
16 000–17 900	1,8 %	3 " (6 %)
18 000–19 900	1,1 %	1 " (2 %)
	96,8 %	54 cases (100 %)

Table 16 gave the total expenses of various kinds incurred by all the parents in 1954. The amount of *expense incurred by each individual parent or guardian* will be seen from Table 18. Information was provided in 59 cases. It is seen that many had no extra expense (39 per cent), and that in most cases expenses amounted to between kr. 100 and kr. 1000 (approximately $ 14.00 and 142.00). In some cases expenses amounted to as much as kr. 2,500 (approximately $ 357.00).

Table 18.

Extra expenses incurred by parents or guardians in 1954 due to children suffering from cerebral palsy.

Expenses	Number of parents or guardians
0	23
Under kr. 100	4
From kr. 100 to kr. 199	6
" " 200 " " 499	14
" " 500 " " 999	6
" " 1 000 " " 1 499	3
" " 1 500 " " 1 999	0
" " 2 000 " " 2 500	3
	59

Table 19.

Occupation of parent or guardian.
(73 cases.)

Occupational group	Distribution percentage for Norway 1950 (whole population)	Parent or guardian of child with c. p. in Østfold	
		Number	Percentage
Agriculture, fishing, forestry .	26	15	20,5
Trades and industry	26	26	35,5
Building and construction work	9	2	3
Transportation	10	5	7
Commerce	11	5	7
Public and private services ..	16	17	23
Other occupations	2	3	4
	100 %	73	100 %

Table 19 gives the distribution of *occupation of parent or guardian.* There is a distinct preponderance in the trades and industry category. That is to

say, there are most children with cerebral palsy in families supported b workers in Østfold (35.5 per cent). The condition occurs relatively fr quently in the category of "public and private services" (public servant independent occupations). The case material of this study (77 cases from Øs fold) is far too small to allow of any general conclusions, however.

While the care of one child with cerebral palsy—in families with onl that one child—should be manageable, the situation becomes more complicate if there are several children in the family. The disabled child may nee extra care. As mentioned earlier, it is preferable for the child to live at hon during treatment. However, sometimes the mother and child have a lon way to travel for treatment, often a number of times a week. The mor children there are in the family, the more difficult it will be for the mothe to find time for this. This was found to be a common situation among th families in Østfold. Table 20 shows how many children there are in eac family. Separate figures are given to show the number of children younge than the patient in each family.

Table 20.

Number of children in families with a child suffering from cerebral palsy.

Number of children in family:	Number of families:	Number of families with children younger than the patient:
1	19	0
2	29	14
3	15	7
4	6	4
5	2	0
6	1	1
7	1	1
8	1	1
12	1	0
	75	28
Not known	2	

It is seen from this table that in most cases (56 out of 75) there were several children in the family. Only in 19 cases was there one child only—the child with cerebral palsy. In the remaining cases there were between 2 and 12 children in the family, and in as many as 28 cases the mother had children younger than the patient.

In summary, cerebral palsy occurs most frequently in Østfold in the children of workers and people employed in public or private services. In 52 per cent of cases their income is between kr. 8,000 and kr. 11,900. In most cases (75 per cent) there is more than one child in the family, and the extra expense incurred on account of the child's disability usually is between kr. 100 and kr. 1000 for a year.

CHAPTER X

FUTURE WORK FOR THE BENEFIT OF CHILDREN SUFFERING FROM CEREBRAL PALSY

The previous chapters have given an account of various aspects of cerebral palsy in one of the counties in Norway. The results of this enquiry should serve as a basis for planning the future work to be done on the problems in Østfold county. If one attempts to apply the conclusions drawn from the situation in Østfold to Norway as a whole, it has been pointed out that reservations should be made on a number of points. In order to be more representative, an enquiry of this kind should also include one of the northern counties and also a county in the center of the country. But the more general conclusions justified by this enquiry apply just as well to the rest of the country as to the single county of Østfold.

Prevention.

The physical conditions under discussion here can never be cured entirely. We can only reduce their consequences as much as possible, and reduce invalidism to the greatest possible extent. Therefore it is of particular importance to try to *prevent* the condition from occurring.

In about 90 per cent of the cases the etiological factors operated before or during birth, while only 10 per cent were caused later. Supervision of the mother's health during pregnancy is of the utmost importance in preventing illnesses which may injure the foetus (virus diseases, anæmia, toxemia and so forth). Further, delivery should be in skilled hands; this is important in preventing injury to the mother or to the child. It is also important to take note of the child's condition immediately after delivery, so that the appropriate treatment can be administered rapidly if there are any pathological signs. Erythroblastosis fetalis is an example of a condition where there is some possibility of *preventing* the occurrence of cerebral palsy if the mother is correctly supervised during her pregnancy and the child is carefully observed by a skilled staff for some time after birth.

Careful medical supervision during pregnancy and delivery at a maternity home or hospital which is staffed with skilled obstetricians are of great importance in the prevention of cerebral palsy. The former should be possible in most places in Norway. Delivery cannot always, for practical reasons, take place under the most favourable conditions. It is to be hoped that the state of affairs can be improved to the point where at least all expectant mothers who are *expected* to have a pathological delivery are sent to special maternity homes. The services of a pediatrician also should be available at such homes.

In order to prevent cases arising *after* birth (meningitis, encephalitis, brain trauma and so forth), adequate treatment of the diseases and injury likely to give rise to cerebral palsy must be given in time.

Early diagnosis of cerebral palsy.

To obtain the best possible results in treating these children, treatment must begin as early as possible. But the *prerequisite* of early treatment is early diagnosis. Among other things, early diagnosis depends upon an examination by a specialist of every child whose mother has been ill during pregnancy, and of every child whose birth has been pathological. In doubtful cases, the child also must be kept under constant supervision by a specialist. This should be possible when the Directorate of Health's plan for pediatric consultants in connection with the office of county medical officer is put into practice. *(Directorate of Health P. M. 5053/52.)* All such cases would then be compulsorily reported to the county medical officer, and they could then be summoned to the consultant for a check-up at regular intervals, at least for the first two years of life. He could then direct them to be admitted to special hospitals for closer examination if necessary.

Treatment of cerebral palsy.

Various problems connected with the treatment of cerebral palsy were discussed in Chapter 6. In deciding how large a treatment center for the county of Østfold should be, a number of factors need to be considered.

1. There must be room for all patients for whom treatment on an out-patient basis is impracticable, either because the case is too severe or because several forms of treatment are needed simultaneously. It will be seen from table 13 that 22 patients are of this type.

2. There must be room for a number of less involved cases whose *home conditions* make out-patient treatment impracticable, or who *live too far away from the place of treatment*, making it essential for them to be admitted as in-patients.
3. On the one hand, the treatment center must not be so large that it loses the character of a home. But there must be a sufficient number of patients to provide full employment for the various therapists, so that the valuable services (physiotherapy, occupational therapy, nursery school, speech therapy, teaching) are used to the best advantage.
4. An important factor in deciding the need for in-patient accommodation is the *duration of the stay* of each child. As soon as the patient is well enough, he should be sent home and continue treatment as an out-patient. It is not possible at the present time to give figures with regard to duration of residency in treatment centers. A large number of children have to be treated and observed for some time—several years.

The following plan may serve as a provisional program for the county of Østfold.

If due consideration is given to the factors mentioned above and to the needs as indicated in Tables 12 and 13, a treatment center for the county of Østfold should have 25 beds. Fifteen of these should be for children *under* school age and 10 children *of* school age. With this number of beds it should be possible to send patients home or admit new ones as needed.

The following staff with a special training in cerebral palsy should be provided:

2 physiotherapists
1 nursery school teacher
1 occupational therapist
1 speech therapist
1 teacher
1 doctor

Apart from the speech therapist and the doctor, the whole staff would be employed full-time at the center. The speech therapist would take care of other cerebral palsy cases needing treatment as out-patients.

The desirable geographical location of the treatment center is apparent from Fig. 1. It should be as central as possible so that travel to the center would be as short as possible, for case admission, check-ups, and visits by parents. (The logical site would be in the Fredrikstad–Sarpsborg district.)

It has been pointed out already that *out-patient treatment* of children with cerebral palsy requires a great deal of time and labor on the part of the parents. The largest share of the responsibility usually goes to the mother, consisting of taking the child to the therapist from one to three times a week, in addition to giving the child treatment at home. Further, the child often has to be fed, dressed and looked after to a much greater extent than other children. It is obvious that all this will take much of the mother's time. If there are several children in the family, adequate treatment hardly can be provided. It has been observed that home treatment is seldom entirely successful. A way must be found to save the mother's time and to make treatment more effective. This could be done by employing a physiotherapist who has been specially trained in cerebral palsy to serve the whole county. Her duties would consist of travelling to the homes of cerebral palsied children, giving treatment in the homes and at the same time training the mother in how to give the treatment, seeing that this is done correctly. Probably each individual child would receive treatment less frequently if this method were adopted, but it would save time for the mother and insure better supervision, for the physiotherapist would see what conditions and possibilities the home had to offer.—In cases where the mother is incapable of this work, an attempt must be made to get some suitable person in the neighbourhood to take over the mother's part in the treatment of the child. This person would then be trained by the physiotherapist. An appeal could be made to older, intelligent mothers of grown-up families, whose work in the home now takes less time. These women must be interested in social and humanitarian work, and willing to take on this responsibility. A system of payment for this would have to be worked out.—Successful out-patient treatment would reduce the cost of treatment, and from a psychological point of view, it would be a great advantage in that the children would not have to be away from home for such long periods that they got out of touch with their parents.

All medical examinations of both in- and out-patients should be given by the doctor in charge of the treatment center, so that the beds available there are used by the children most in need of in-patient treatment at the time. The doctor may be a neurologist, orthopedist or pediatrician, specially trained in cerebral palsy.

Before these children qualify under the county arrangements for treatment, often they have had to undergo special examinations, partly for diagnosis and differential diagnosis, and partly as part of treatment. Ideally these examinations should be made at large central hospitals well provided with

equipment (X-ray, electroencephalograph, and so forth) and specially trained staff. These should be places such as children's hospitals, which have good access to both neurological and orthopedic services. It would be ideal to have a center for treatment, of the size suggested for Østfold, in close contact with such a children's hospital. Cases should be admitted for "charting" first. Those presenting special treatment problems (surgical cases, problems connected with braces, and so forth) also should be treated at the center. This institution would need the same types of therapists as suggested for Østfold, but the medical service should be enlarged to include a neurologist, orthopedist and pediatrician. A central institution of this nature also would need the assistance of a psychologist and social service worker, and a psychiatrist also.

Schooling and training did not present much of a problem in the case of Østfold. In general this aspect of treatment should be handled for larger areas through one training center—as has already been suggested (p. 42). Such a center could meet the needs of individuals who are restricted in their choice of occupation.

There will be some need for *nursing home care* for children with cerebral palsy, disabled or some mentally defective. Judging from the situation in Østfold, Norway as a whole would need about 80 places in homes for the disabled and 300 places in homes for mental defectives. In many instances in both types of case parents both *can* and *will* keep their children at home. However there will still be quite a large demand for such an accommodation. Mentally defective cases should be treated in special homes attached to the central institutions for mental defectives as described in the national plan for the care of mental defectives.

Legislation.

The various legal provisions applicable to cerebral palsy have been described already. The question is whether these provisions are adequate for existing needs. On the whole, they are, but full use is not being made of them for the benefit of patients. It has already been shown how the duty of reporting cases by doctors is neglected. Further, parents and guardians are not well enough informed on what has been done to help them. In this connection, some skilful social service work is needed.

It should be made compulsory to report cases of special illnesses during pregnancy and pathological deliveries. The children involved should be examined regularly by a specially trained doctor.

Disablement relief should not be restricted to young people over the age of 16. Totally disabled children also should be entitled to it.

A particularly difficult problem is the type of children who are not mentally defective, but whose injuries are so severe that there is little hope of any tangible progress. If these children are to be put into nursing homes, the insurance companies are not obliged to pay for their care. No provision is made as to how the cost is to be covered. Legislation regarding payment for their stay in nursing homes must be introduced, similar to the plan for mental defectives (p. 44).

Finally, it should be mentioned that since 1956 there has been an improvement in the situation of parents or guardians in regard to income tax. They may now claim assessment in a lower tax class in the case of between 50 per cent and 79 per cent invalidism, and two classes below in the case of at least 80 per cent invalidism.

SUMMARY

Chapter 1.
Introduction.

The introduction gives a definition of the term infantile cerebral palsy, and attention is drawn to the various conditions which must not be confused with it. It is emphasized that cerebral palsy is not a single disease, but a group of conditions resulting from brain injuries. These conditions are grouped together for practical therapeutic purposes.

The development of therapy for cerebral palsy children is described briefly and an outline is given of the problems to be discussed in this paper.

Chapter 2.
Incidence.

In enquiring into the *incidence* of infantile cerebral palsy in the county of Østfold, the author has found *84 cases under the age of 21.* Seventy-seven of these have formed the nucleus for a study of various aspects of this condition.

The geographical distribution of cases in the county is examined (Table 2 and Figure 1), together with their distribution according to age (Table 3).

It is calculated that on an average *3.6 infants are born annually per 100,000 inhabitants in the county*, which means that there are approximately *1.9 cases of cerebral palsy per 1000 births.* The condition seems to occur considerably less frequently in Europe than in the U.S.A. (Table 4).

Assuming that the figures for Østfold are representative of Norway as a whole, the following estimate is obtained:

119 children are born with cerebral palsy in Norway each year.

The number of cases of an age suitable for treatment (under 21) is judged to be either 1,500 or 2,300, according to whether calculations are based on the total number of cases found in Østfold, or on the 5—9 age-group.

It is the *duty of doctors to report all cases*, but this has very seldom been done. As a result, only a few of the cases have been registered.

Chapter 3.

Classification according to type.

The case material is divided into the usual clinical types, and their distribution (Table 5) tallies almost exactly with the results of corresponding enquiries in the U.S.A. (Pohl).

As to the degree of severity of the cases (Table 7), not quite half were moderately involved, a fourth were severe, and a third were mild cases.

Chapter 4.

Causes or cerebral palsy.

The various circumstances that may have caused patients to have cerebral palsy, or which are assumed to be the cause of it in some cases, were investigated. The cases are divided into categories according to the time, in relation to birth, when the injury is thought to have occurred (Table 8).

Chapter 5.

Diseases and defects evident in conjunction with infantile cerebral palsy.

The various conditions which may accompany cerebral palsy and complicate treatment are listed. An estimate of the patients' *intelligence* is given (Table 10): more than half (60 per cent) were assumed to be of about normal intelligence. Their *speech ability* (Table 11) is shown. Somewhat more than half (57 per cent) had speech defects. *Epilepsy* was present in the anamnesis of $^1/_3$ of all cases. *Visual disorders* occurred in 17 cases (22 per cent) and *auditory disorders* in only one case.

Chapter 6.

Problems connected with treatment.

First the types of treatment which are believed to be necessary for all the patients in Østfold are described, and than compared with the extent to which such types of treatment have been given (Table 12). The need for various forms of in-patient treatment is discussed. This is compared with the number of cases receiving needed treatment as in-patients (Table 13).

Chapter 7.

Schooling and training.

Most children of school age with cerebral palsy in the county of Østfold receive the schooling they are entitled to as long as they are mentally and

physically capable of it (Table 14). They usually attend ordinary schools and are seldom taught at home. However, more than half of these children attending ordinary schools have difficulty in keeping up (13 out of 20) and must be assumed to be in need of a special school.

The number of young people needing help with vocational training was small; 4 out of 7 patients had decided on their future occupations and were able to obtain training.

Chapter 8.
Financial aspects of cerebral palsy in Østfold.

Enumerations are given of the expenses incurred by the state and local authorities, insurance companies (Table 15), and parents or guardians (Table 16) for the patients' treatment in 1954. Total expenses (not including those connected with mental defectives) amounted to about 50,000 kroner (approximately $ 7,143). Complete treatment for every patient in the county would cost approximately 250,000 kroner (approximately $ 36,000).

Chapter 9.
The child with cerebral palsy and its relation to the family.

The incomes of most parents or guardians in 1954 (Table 17) were between kr. 8,000 and kr. 12,000 (approximately $ 1,142.00 and 1,700.00). In most cases their expenses were under kr. 1000 (approximately $ 142.00) (Table 18), and in 39 per cent of cases the parents had no extra expenses on account of the child's disability. In most cases (35,5 per cent) the parents' or guardians' occupation was in trade and industry (Table 19).

In 19 cases the child with cerebral palsy was an only child, and in 56 cases there were between two and twelve children in the family.

Chapter 10.
Future work for the benefit of children with cerebral palsy.

On the basis of this study of cerebral palsy in the county of Østfold a number of suggestions are made in respect to the work to be done in future for prevention, therapy and program administration.

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CHANGES IN BODY WATER COMPARTMENTS DURING GROWTH

BY

BENT FRIIS-HANSEN

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CHANGES IN BODY WATER COMPARTMENTS DURING GROWTH

H. BEHRNDT & CO., BOGTRYKKERI, KØBENHAVN

CHANGES IN BODY WATER COMPARTMENTS DURING GROWTH

BY

BENT FRIIS-HANSEN

EJNAR MUNKSGAARD COPENHAGEN

1956

Denne afhandling er i forbindelse med omstående tidligere publicerede afhandlinger af det lægevidenskabelige fakultet ved Københavns universitet antaget til offentligt at forsvares for den medicinske doktorgrad.

København, den 3. juli 1956.

P. Bonnevie
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1. Schloerb, Paul R., Bent J. Friis-Hansen, Isidore S. Edelman, A. K. Solomon and Francis D. Moore, The measurement of total body water in the human subject by deuterium oxide dilutium. With a consideration of the dynamics of deuterium distribution. *J. Clin. Invest.*, 1950, 29: 1296.
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PREFACE

The work described here was commenced in Boston, U.S.A., in 1948, while I was Research Fellow in the Departments of Surgery and Paediatrics, Harvard University, at the Peter Bent Brigham Hospital and the Children's Medical Center.

At the time of my visit Dr. Francis D. Moore, Moseley Professor of Surgery, and his colleagues were developing their pioneer studies on the composition of the body and the metabolic response to surgery. I was most fortunate in being invited to join this team and in being able to commence this work in the Surgical Laboratories of the Peter Bent Brigham Hospital. I shall always be grateful for the profitable and happy two years I spend there.

When the method for the determination of total body water had been perfected, I was given the opportunity to study children in the Children's Medical Center, where I worked with the team led by Dr. James L. Gamble.

After my return to Denmark in 1950, I was able to continue the work while holding the post of Clinical Assistant to Professor Dr. med. Preben Plum in the Department of Pediatrics, Rigshospitalet, University of Copenhagen. Here I was able to extend the studies so as to include measurements of the extracellular water. I carried out the heavy water determinations in the Department of Biological Isotope Research, University of Copenhagen, by courtesy of Professor Dr. phil. Hans H. Ussing.

I wish to express my warmest thanks to the heads of all these Departments for the great kindness they always have shown me and the inspiration they have been to me, and for the ideal working conditions they have provided for me.

My thanks are also due to Dr. Charles A. Janeway and to Dr. Clement A. Smith and to Professor Dr. med. Erik Rydberg for the permission to study infants and children at the Children's Medical Center, Boston, at the Boston Lying-in Hospital and at the Lying-in Department A, Rigshospitalet, Copenhagen.

My friends and collaborators at various stages in this study have been Drs. Isidore S. Edelman, Malcolm A. Holliday, Francis D. Moore, Paul R. Schloerb, David B. Sheldon, Thomas Stapleton, Georges Stoll, Folke Tudvad, Jørgen Vesterdal and William M. Wallace.

The statistical sections have been made in collaboration with cand. act. Michael Weis Bentzon and mag. scient. Ove Frydenberg.

Dr. Thomas Stapleton has helped in the preparation of the english version of the manuscript.

Mrs. Gunver Nissen has helped as secretary, Mrs. Bodil Folmer Jensen as technical assistent and Miss Anna Margrethe Overgård has prepared the graphs.

I want to thank all these people for their valuable contributions and construtive criticisms.

Finally I must acknowledge my debt to the children whom I have investigated.

Support for this work has been generously provided by: Peter Bent Brigham Hospital, American Scandinavian Foundation, P. Carl Petersens Fond, Kong Christian den Tiendes Fond, Carlsbergfondets Universitetslegat, Mrs. Marianne Malthe-Bruun and Miss Helga C. Melchior.

Copenhagen, September 1955. BENT FRIIS-HANSEN

CONTENTS

KEY

T = total body water in liters = the deuterium oxide volume of dilution.

E = extracellular water in liters = the thiosulfate volume of dilution.

I = intracellular water in liters = calculated as T – E.

H = body length or height in centimeters.

W = body weight in kilograms.

SA = body surface area in square meters.

A = age in years.

AGE GROUPS

I = 0 to 11 days.

II = 11 days to ½ year.

III = ½ year to 2 years.

IV = 2 years to 7 years.

V = 7 years to 16 years.

ERRORS

p. 28, (10): $- - - + \beta_h - b_h) \cdot (h - h) + y$

read $+ (\beta_h - b_h) \cdot (h - h) + y$.

p. 41, table 17: E/SA in % read E/W;

p. 51, table 21: 1–10 days read 1–30 days;

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La méthode expérimentale n'est, en définitive, que la logique appliquée à la coordination des phénomènes de la nature pour en découvrir les lois. Claude Bernard.

Chapter 1.

INTRODUCTION

An interest in the fluids of the human body is as old as the study of medicine itself. Yet, for hundreds of years no attempt was made to measure or to obtain detailed information about these important constituents of the body.

The place of water in the body is unique and its functions are legion: it is the largest single component of the body, it is the medium in which enzymatic reactions take place, electrolytic dissociation is (with few minor exceptions) only possible in a water medium, water acts as a solvent and a lubricant, and it enables solvents and heat to be transported. In brief, it may be said that life and the universe around us is a function of the physical and chemical properties of water.

The early Greeks described life as water and fire. Water, together with fire, air and earth, were considered to be the four elements of nature, and Greek physicans developed the "humoral pathology", where all diseases were ascribed to some imbalance of the body fluids.

There are a few scattered remarks about water metabolism to be found in the ancient litterature. Some of these are in close agreement with the latest results of modern science.

Hippocrates (about 400 B.C.) wrote thus that, "a child is blended of moist, warm elements, because of these he is composed and in them he grew. The moistest and warmest are those nearest to birth".

Galen (about 150 A.D.) made a similar statement, "for always, from his birth, every animal daily becomes drier, but not equally warmer and cooler at all ages".

That growth is associated by a decreasing water content seems to have been a generally accepted concept. This has also later been stated by Razes (about 900 A.D.), who added that the blood of children in the same fashion contained more moisture than that of adult and old people.

Much later Tobias Katz, a Hebrew doctor, who lived around 1700 A.D. said that it was the nature of children to sleep, because of the greater amount of fluid in them.

During the Renaissance a friend of Galileo, Sanctorius (1614) by name, measured the weight of food and drink taken daily and compared this with the weight of urine and feces discharged. From these data and the variations in

his body weight he deduced "the quantity of material lost by insensible transpiration through the skin and lungs". This seems to be the first balance study ever done.

Actual measurements of the amount of water in the body were not carried out until a hundred years ago, when the young analytical chemists under the inspiration of Liebig, investigated the chemical composition of plants and animals and later compared the constituents of food to those of the human body. Such determinations were first carried out by v. Bezold (1857) and by Bischoff (1863).

Their results and other data collected during the later part of the last century have served as a basis for modern physiology until twenty years ago; then isotopes were introduced as a tool in clinical investigation. This has made in vivo measurements of different body constituents possible and led to a growing interest in body composition in health and disease.

At the same time, fluid replacement therapy has become a generally accepted and widely used form of treatment. The focus of interest has recently turned from the composition of extracellular fluid to that of the cells, which is a further important step forwards.

Nevertheless, our knowledge of the static and dynamic states of the different body fluids is stille meager, even in the normal subject. This study was undertaken to clarify some aspects of the changes in body water compartments during growth.

BODY WATER COMPARTMENTS

The water in the body may be divided into several compartments or subdivisions.

Total Body Water includes all water in the body, both water inside and outside the cells of different tissues, as well as the water normally present in the gastro-intestinal tract, the urine and other secretions.

Total body water is divided into two main compartments: *Intracellular Water* and *Extracellular Water*.

This division of the body fluids is fairly new. In his book about body fluids Claude Bernard in 1859 listed a number of different fluids of the body, which he divided into: the circulating fluids, the more stationary fluids that are special for each tissue and those formed during pathological conditions. However, he did not describe whether the fluids were found outside or inside the cells, but his list includes mostly extracellular fluids: blood; lymph; interstitial fluid; the secretions of different glands including bile, sweat and milk; urine; water in the gastro-intestinal tract, the eye and the serous cavities and pus. This grouping is based upon anatomical boundaries; each includes a number of fluids of different properties and does not make any physiological entity.

Intracellular Water includes all water inside the cells of the body and is separated from the surrounding fluid by the cell membrane, which is freely permeable to water.

The *Anatomical Extracellular Water* is by definition all body water outside the cells, but several subdivisions exists, both anatomical and functional. In contrast, the *Physiological Extracellular Water* may be defined as the water of plasma and of fluids into which ions and small molecules diffuse freely from the plasma, i.e. liquids which are composed like a plasma ultrafiltrate, namely plasma and interstitial fluid. By this definition, water in the gastro-intestinal tract and the secretions are excluded as well as water in the serious cavities and the eye humors (Manery, 1954). The term *Transcellular Water* has recently been proposed by Edelman, Olney, James, Brookes & Moore (1952) for this lastnamed sub-group of extracellular water, since extracellular water has to cross cell membranes other than capillaries to reach these areas.

The *Anatomical Extracellular Water* may thus be divided into the *Physiological Extracellular Water* and the *Transcellular Water.* The latter will then by definition include *Water in the Gastro-Intestinal Tract,* which equally well might be taken as a third group due to its execptional composition and its location. In a way it can be considered as being outside the body. It is a mixture of water taken by mouth, partly digested food and the digestive secretions. The daily volume of these secretions in the adult totals 6 to 8 liters, which normally is reabsorbed nearly completely. This volume is almost as large as that of the extracellular fluid and the whole process is an important example of the "transcellular circulation" of extracellular fluid.

However, the whole concept of intra- and extracellular fluid may well need a revaluation, as the rapidly growing knowledge of the nature of the cell membrane shows that the cells are in a dynamic steady state, where the "membrane" is permeable to many of the extracellularly located ions. The old concept of iso-osmolarity inside and outside the cells may not be valid in spite of the free movement of water. Recent investigations have shown that certain structures inside the cells, such as the mitochondria, seem to play a central role in the water and electrolyte metabolism of the cell.

The theory has even been put forward by Ling (1952) that the cells are not surrounded by a "membrane", and that the separation of different ions such as sodium and potassium is accomplished by the physical properties of the cell-proteins in connection with the different dielectric contants of hydrated K^+ and hydrated Na^+.

The rapid rate at which water is exchanged between plasma and tissues has recently been studied by the use of different "isotopes of water" by Edelman (1952) and by Lilienfield, Freis, Partenope & Morowitz (1955), and the whole problem of water exchange between the body and external environment as

well as exchange inside the body has been reviewed by Pinson (1952). Great variations have been found in the time necessary to obtain equilibrium. In the erythrocytes this is obtained in less than 1 second, whereas a much longer time, 2 to 3 hours, is taken in bone (Edelman et al. 1954). From the viewpoint of the present study it is of importance that all these studies support the underlying principles used in the determination of both total body water and of extracellular water: a rapid exchange between plasma, interstitial and cell fluids.

Eminent books about the physiological aspects of body fluids have been written by John P. Peters: The Exchange of Fluids in Man (1935) and by James L. Gamble: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid (1942), and an extensive survey has just been published by Elkinton and Danowski: The Body Fluids, Basic Physiology and Practical Theraputics (1955).

METHODS

METHODS FOR THE MEASUREMENT OF TOTAL BODY WATER

The first determinations of total body water in the human subject were carried out by v.Bezold in 1857 and by Bishoff in 1863. These classical studies were carried out by desiccation and later investigators have used a similar technique up to the present time. By this technique the water content is calculated from the "wet-weight" and the "dry-weight". The latter is obtained by heating in an oven at a constant temperature around 100° C. to constant weight. Although theoretically simple many practical difficulties are encountered during this procedure. First, if the object is of large size it has to be cut into pieces before drying and during this process an appreciable amount of water evaporates and blood and tissue particles are lost, whereby an error of several per cent may be introduced. Secondly, fat and proteins may form hard, impermeable scales that will retain some water. To avoid this, fat extraction has to be carried out, leading to further errors.

When, however, due precautions are taken, accurate results are obtainable and this method is still widely used, especially in animal experiments and in histochemical studies.

In vivo measurements are of greater interest to the clinician and may be carried out by: 1) balance studies of water and electrolytes, 2) determination of the specific gravity of the body, and 3) dilution of isotopic water and various water soluble substances, which are uniformly distributed in body water and insoluble in other body constituents.

1) In the human subject total body water has been calculated from the relation between water and electrolyte intake and output (Lavietes, D'Esopo & Harrison, 1935), but this method is rather troublesome and inaccurate.

Total body water has also been estimated in the cat by Hetherington (1931) from changes observed in the osmotic pressure of the blood after intravenous injection of hypertonic saline. The volume of distribution of large water loads was studied by Leaf et al. (1954), who found values equal to total body water.

2) It has been shown that the body may be divided into a fat-free portion: "Lean Body Mass", and a variable amount of "fat-tissue", and that this lean body mass has a constant gross composition with 73.2 per cent of water (Moulton, 1923 and Behnke, 1941). It follows that the amount of fat in the body may be calculated from total body water (Pace and Rathburn, 1945) as

$$\%\ \text{fat} = 100 - \frac{\%\ \text{water}}{0.732}$$

The fat content may also be calculated from the specific gravity of the body (Rathburn and Pace, 1945) as

$$\%\ \text{fat} = 100 \cdot \left(\frac{5.548}{\text{sp. grv.}} - 5.044 \right).$$

From these equations it is seen that a close correlation exists between body water and specific gravity:

$$\%\ \text{water} = 100 \cdot \left(4.317 - \frac{3.960}{\text{sp. grv.}} \right).$$

This has been verified in a large series of experiments on adult men by Messinger & Steele (1949) and by Osserman, Pitts, Welham & Behnke (1950). These authors have, however, used 71.8 per cent as the water content of lean body mass, a figure which they arrived at from measurements of total body water with antripyrine.

A very similar result was obtained by McCance & Widdowson (1950) in their studies on body composition. Their calculations were based on determinations of total body water by the urea-method; they found a water content of 71 per cent of lean body mass, but as they pointed out, the calculation of body fat from body water is only valid when the proportion of extracellular fluid is equal to that found in the normal adult. For this reason these equations are not suitable for use in young children, and obviously it does not make sense to apply the first formula to a subject with a water content higher than 73.2 per cent.

3) The principle of the dilution method is that a known amount of a test substance is injected and when a uniform distribution in all body fluids has taken place the volume of dilution may be calculated from the equilibrium concentration. The equation for this relationship is:

$$\text{I} \times \text{C} = \text{T} \times \text{C}_{\text{eq}} - \text{A}$$

where: I = volume injected; C = concentration of the injected substance; T = total body water; C_{eq} = equilibrium concentration in body fluids; A = amount lost during the equilibration period.

Different substances have been tried out for this purpose: urea (Marshall & Davis, 1914 and Steffensen, 1951); sulfonamide (Painter, 1940); thiourea (Danowski, 1944); antipyrine (Soberman, Brodie, Levy Axelrod, Hollander & Steele, 1949); and later a derivate of antipyrine, NAAP, has been recommended (Brodie, 1951).

All these substances have in common that they are metabolized during the equilibration period, for which reason "isotopes of water" are preferable. The most used are: deuterium oxide (heavy water, D_2O) (Hevesy & Hofer, 1934) and tritium oxide (radioactive water, T_2O) (Pace, Kline, Schachman & Harfenist, 1947).

The proporties of these isotopes and the theory for their use have been discussed recently by Schloerb, Friis-Hansen, Edelman, Solomon & Moore (1950) and by Pinson (1952), and it is concluded that in spite of the heavier molecular weight these isotopes behave like ordinary water in the body when they are present at low concentration. Tritium is radioactive and is a soft beta particle emitter of about 0.018 mev. maximum energy and a half life of about 12 years. Because of the radiation hazard, it is not suitable for work in children.

Deuterium is not radioactive and heavy water is non-toxic in concentrations lower than 25–30 per cent. It has therefore been selected for this study and used as previously described. (Schloerb, Friis-Hansen, Edelman, Solomon and Moore, 1950). Deuterium has the mass two and heavy water has a specific gravity which is about 10 per cent higher than ordinary water.

The measurements of heavy water in body fluids were carried out in Boston by the falling drop method (Schloerb, Friis-Hansen, Edelman, Sheldon & Moore, 1951) and by the mass spectrometer (Solomon, Edelman & Soloway, 1950), and in Copenhagen by the gradient tube method (Friis-Hansen, 1954).

When isotopes of hydrogen are used, an error is introduced due to an exchange with labile hydrogen atoms of the solid constituents of the body, mainly the proteins. The measured volume of dilution will therefore be estimated as 0.5–1.5 per cent higher than the actual water volume. The theory of the calculation of this exchange has already been discussed by Schloerb, Friis-Hansen, Edelman, Solome & Moore (1950).

Later studies by Prentice, Siri, Berlin, Hyde, Parsons, Joiner & Lawrence, (1952) have also shown that the tritium oxide volume of dilution is about 2 per cent higher than the actual water volume measured by desiccation and 2.3 per cent higher than the antipyrine volume. A similar difference, 1.8 per cent, was found between the deuterium oxide volume and the antipyrine volume in children (Friis-Hansen, Holliday, Stapleton & Wallace, 1951), whereas

Ljunggreen (1955) found the deuterium volume higher by 9 per cent. This experimental evidence supports the theoretical calculation.

In spite of this no correction of the deuterium space has been applied, since the exact value of this correction depends upon factors that are variable and have not been measured separately in the subjects. For similar reasons any correction for urinary loss has not been carried out.

The term *"Total Body Water"* has been used in this study to denote the uncorrected volume of dilution of heavy water.

METHODS FOR THE MEASUREMENT OF EXTRACELLULAR WATER

No ideal method has been found for the measurement of extracellular water. An ideal substance for this determination should distribute itself, after injection, evenly throughout the entire extracellular compartment, without penetrating any cells, and should be present in all areas at a concentration equal to that of a plasma ultrafiltrate. Furthermore, the substance should not be metabolized or excreted until equilibrium had been reached, and should neither be toxic nor have any osmotic or diuretic effect.

It is evident that all these claims cannot be fulfilled at the same time: an inert substance like inulin, that presumably does not penetrate into any cells, is for the same reason excreted through the kidneys at a rapid rate since it is not re-absorbed by the tubular cells, and since diffusion into the interstitial fluid is slow and excretion is fast, complete equilibrium will never be obtained. On the other hand a compound like thiocyanate is slowly eliminated from the body, because it is re-absorbed by the kidneys and consequently enters the tubular cells as well as other glandular cells.

A great number of compounds have been tried. These may be grouped into electrolytes and non-electrolytes.

The electrolytes which have been used most are: thiocyanate (Crandall & Anderson, 1934), sulfate (Lavietes, Bourdillon & Klinghoffer, 1936), bromide (Wallace & Brodie, 1939) and thiosulfate (Gilman, Philips & Koelle, 1946). Lately radioactive substances have been used: sodium (Kaltreider, Meneely, Allen & Bale, 1941), chloride (Winkler, Elkinton & Eisenman, 1943), bromide (Eliel, Pearson & Rawson, 1950) and sulfate (Walser, Seldin & Grollman, 1953).

As non-electrolytes, different carbohydrates have been used: mannitol (Newman, Bordley & Winternitz, 1944), inulin (Kruhøffer, 1946) and sucrose (Deane, Schreiner & Robertson, 1951).

Of all these methods the "inulin volume of dilution" is generally accepted as the best estimate of the "physiological extracellular volume", since it does not include most of the transcellular water; but due to the rapid excretion and slow distribution the technique it rather elaborate, as it requires a constant in-

travenous infusion for 4 to 6 hrs. and collection of the urine during the following 24 hrs. (Gaudino, Schwartz & Levitt, 1948). The method is therefore not suitable for investigations in children. Furthermore, even inulin has been shown to disappear from the extracellular fluid of anuric subjects (Finkenstaedt et al. 1953), indicating some extrarenal clearence.

The same holds good for other non-electrolytes.

Due to the radiation hazard it is safest not to administer radioactive compounds to children, although modern methods have made it possible to carry out such determinations with very small amounts of activity.

Thiocyanate has been used extensively, although it has been shown that it suffers from several disadvantages: it is bound to lipids (Rosenbaum & Lavietes, 1939) and to proteins (Scheinberg & Kowalski, 1950). During febrile conditions the thiocyanate volume may approach that of total body water, presumable due to permeability changes of the cells (Overman, 1946 and Doxiadis & Gairdner, 1948). But its ease of determination has led to its frequent use as a test substance. The volume of distribution of thiocyanate has been found to be close to the chloride space (Lavietes, Bourdillon & Klinghoffer, 1936) or even larger (Winkler et al. 1943).

Sulfate and thiosulfate have been found to remain almost exclusively extracellular (Bourdillon & Lavietes, 1936), but these substances suffer from the disadvantage of rapid urinary excretion for which reason a correction has to be introduced, either by estimating the urinary loss during the equilibrium period or by calculating the "initial concentration" from the disappearence curve (Cardozo & Edelman, 1952).

In spite of these shortcommings the thiosulfate method has been used for this investigation because of low toxicity and ease of determination in capillary blood. The method used has been described previously (Friis-Hansen, 1954).

Several comparisons between thiosulfate and other methods have been made. Schwartz (1950) found the thiosulfate volume equal to that of mannitol in 2 human subjects; Raiz, Young & Stinson (1953) observed in nephrectomized dogs that the ratio between the inulin and the thiosulfate volume was 0.76 whereas the sucrose/thiosulfate ration was 0.86, and Nichols, Nichols, Weil & Wallace (1953) measured the inulin/thiosulfate ratio to be 0.79 in nephrectomized dogs. The most extensive study of this kind has recently been made by Swan, Madisso & Pitts (1954), also in nephrectomized dogs. They found that the average volumes of dilution were: inulin: 16.0 per cent of body weight, raffinose: 19.4 per cent, sucrose: 21.2 per cent, thiosulfate: 22.4 per cent, radiosulfate: 22.6 per cent and mannitol: 22.6 per cent. The radiochloride space was even larger, about 27 per cent. They concluded that the best estimate of extracellular fluid (without transcellular fluid) was obtained by: mannitol, thiosulfate and radio-sulfate. Similar results have been obtained in man

by Gamble et al. (1953) who found the sucrose volume to be 77 per cent of the radiochloride space.

From these and other experiments it is seen that thiosulfate measures a volume that is 10 to 20 per cent larger than the inulin volume,*) and that thiosulfate, radioactive sulfate, mannitol and sucrose seem to be diluted to almost equal volumes, which correspond to approximately 80 per cent of the chloride volume. This is consistent with the observation that inulin diffuses very slowly into dense connective tissues such as tendons, and much slower than the smaller molecules of thiosulfate and chloride (Kruhøffer, 1946 and Cotlove, 1954). On the other hand it has been observed that some 20–40 per cent of the body chloride is outside the extracellular phase (Deane, Ziff & Smith, 1952). Thiosulfate, radioactive sulfate, mannitol and sucrose are therefore believed to measure the extracellular volume, not including the transcellular volume. This assumption is also supported by the finding that thiosulfate is not absorbed from the gastro-intestinal tract to any appreciable extent (less than 5 per cent) and only traces are excreted into the gastric juice after i.v. injection. (Friis-Hansen, 1953).

The mechanism of equilibration in extracellular fluid has been reviewed by Cotlove (1954). He concluded that the process of distribution of substances in extracellular fluid involves multiple rate components, which do not reflect fixed, anatomically separated components, as the rates of the components and the fraction of extracellular fluid involved varied with different substances and with changes in physiological state. The slowest rate was found in dense connective tissue, and large molecules were more slowly distributed than smaller ones.

Throughout this study the term *"Extracellular Water"* has been used to denote "the thiosulfate volume of dilution", as it is supposed to correspond to the physiological extracellular volume or the total extracellular volume except the transcellular volume.

METHODS FOR THE MEASUREMENT OF INTRACELLULAR WATER

In histochemical studies the total water content is usually measured by desiccation, and if one assumes that all chloride is extracellular, the volume of extracellular water may be calculated from the total amount of chloride, taking the extracellular concentration to be 120 mmol. per liter. The intracellular water may be calculated by subtracting the extracellular from the total amount of water. The intracellular water may also be calculated directly from the total amount of potassium, asuming the intracellular concentration to be 140 mmol. per liter, when a correction has been made for the small amount of potassium in the extracellular fluid. Finally the proportion

*) A formula by which the inulin volume may be calculated from the thiosulfate volume has just been published by Ikkos et al. Acta Phsiol. Scandinav. 1956, 35: 254.

of the cells of a given tissue may be calculated from the "cell solids" which presumably are present at a level of 310 g per kg. All methods have given results that agree satisfactorly.

A very fine discussion of the validity of these calculations and of the underlying principles has been given by Lowry & Hastings (1942), and a close agreement has recently been found between the "volumes" calculated in this way and the corresponding "spaces" estimated directly in histological preparations (Barlow et al. 1954).

Information about the intracellular water volumen in the living subject has only been obtained by subtracting the extracellular from the total water volume. The values of intracellular water in infants and children presented in this study have been calculated by subtracting the thiosulfate volume from the deuterium oxide volume. This volume has been denoted: *"Intracellular Water"*, although this indirect determination only can be considered as a fair estimate of the "True intracellular water", since this calculation is affected by the errors in the measurement of both extracellular and total body water, as described previously.

MATERIAL

The material collected here consists of measurements of *Total Body Water* and/or *Extracellular Water* in 93 infants and children ranging from birth to 16 years of age. A total of 73 determinations of total body water and 51 measurements of extracellular water has been carried out, and in the 31 cases where both total and extracellular water ware measured, the *Intracellular Water* has been calculated by subtraction.

All the observations are listed in table 1 which gives for the subjects: age, sex, body weight, length or height, body surface area (Du Bois) and total body water, extracellular- and intracellular water in liters, in per cent of body weight and in liters per square meter surface area.

As described later the material has been divided into different age groups, and the number of observations of both total, extracellular and intracellular water within each age groups is summarized in table 2.

Some of the total body water determinations were carried out in Boston: 15 were studied at the Peter Bent Brigham Hospital, 18 at the Children's Medical Center and 5 at the Boston Lying-in Hospital. The remaining determinations of total body water and all the measurements of extracellular water have been carried out in Copenhagen at the Rigshospital: 50 at the Department of Pediatrics and 5 at the Lying-in Department A.

Some of these observations have been published before. 23 of the total body water measurements were presented in colaboration with: Malcolm Holliday, Thomas Stapleton and William M. Wallace (Total body water in children,

1951). These observations were extended by a further 15 observations of total body water in children, together with similar observations in young adults, middle-aged and old people in a study of total body water throughout the life span by: Isidore S. Edelman, Harold B. Haley, Paul R. Schloerb, David B. Sheldon, Bent J. Friis-Hansen, Georges Stoll and Francis D. Moore. (Further observations on total body water. 1. Normal values throughout the life span. 1952).

The remaining 35 measurements of total body water have not been previously published.

A summary of the measurements of extracellular water has been given by Friis-Hansen (The extracellular fluid volume in infants and children, 1954).

The observations may be divided into 3 groups as stated in table 2: total body water alone was measured in 42 cases; total and extracellular water simultaneously in 31 cases, whereby intracellular water has been estimated in these subjects, and extracellular water alone was determined in the remaining 20 cases.

All subjects were considerer to be in a normal state of hydration and nutrition at the time of examination, and their body build was evaluated by the variation from the "normal weight" corresponding to the height of the subjects. As a standard of reference the danish normal values have been used. (Lægeforeningens Lommebog 1954 and the tables of Døssing 1952).

The danish normal values are only slightly different from those found in the United States of America (Mitchell-Nelson, Textbook of Pediatrics. 1950).

The deviations from the "normal weight for height" have been calculated in per cent, and as it is seen in figure 1 the subjects show a random distribution around the norm, which indicates that the material is representative.

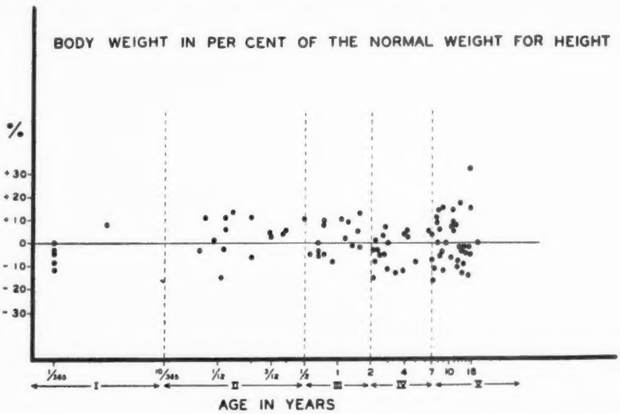

Fig. 1. The body weight of the subjects calculated in per cent of the normal weight for height within the five age-groups. The material shows an even distribution of positive and negative deviations.

TABLE 1

Subject		Sex	Age years	Height cm.	Weight kg.	Surface area sq.m.
Number	1	M	1/365	48	2.95	0.190
»	2	F	1/365	51	3.10	0.200
»	3	M	1/365	53	3.40	0.215
»	4	M	1/365	52	3.47	0.215
»	5	F	1/365	52	3.50	0.215
»	6	F	1/365	52	3.60	0.220
»	7	F	3/365	53	4.03	0.230
»	8	F	10/365	49	3.17	0.195
»	9	F	15/365	48	2.27	0.170
»	10	F	16/365	46	2.38	0.165
»	11	M	21/365	47	2.27	0.165
»	12	F	21/365	54	3.73	0.225
»	13	M	23/365	51	3.90	0.225
»	14	M	28/365	46	2.34	0.165
»	15	M	28/365	56	4.19	0.240
»	16	M	1/12	52	3.06	0.205
»	17	F	1/12	52	3.49	0.215
»	18	M	1/12	52	3.85	0.220
»	19	M	1/12	58	5.34	0.280
»	20	M	1/12	58	5.47	0.280
»	21	M	2/12	59	4.60	0.265
»	22	M	2/12	59	5.12	0.275
»	23	M	3/12	57	4.88	0.260
»	24	F	3/12	58	5.01	0.270
»	25	F	4/12	55	4.22	0.240
»	26	M	4/12	64	6.80	0.330
»	27	M	5/12	64	7.15	0.340
»	28	F	7/12	68	7.52	0.360
»	29	M	8/12	62	5.40	0.295
»	30	M	8/12	69	7.85	0.375
»	31	M	8/12	68	7.90	0.365

urface area sq.m.	Total Body Water liters	% Body Wt.	l/sq.m.	Extracellular Water liters	% Body Wt.	l/sq.m.	Intracellular Water liters	% Body Wt.	l/sq.m.
.190	2.29	77.6	12.05						
.200	2.59	83.5	12.95						
.215	2.71	79.6	12.60	1.36	40.0	6.32	1.35	39.6	6.28
.215	2.75	79.4	12.78	1.51	43.6	7.02	1.24	35.8	5.76
.215	2.59	74.0	12.04	1.37	39.1	6.36	1.22	34.9	5.68
.220	2.98	80.1	13.55	1.90	52.8	8.64	1.08	28.3	5.91
.230	3.18	79.1	13.83						
.195	2.18	68.8	11.18	1.09	34.4	5.59	1.09	34.4	5.59
.170	1.67	73.6	9.82						
.165	1.71	71.8	10.36						
.165	1.89	83.0	11.45						
.225	2.87	77.0	12.76	2.11	56.6	9.38	0.76	20.4	3.38
.225	2.62	67.0	11.66	1.11	28.4	4.94	1.51	38.6	6.72
.165	1.71	73.1	10.36	0.92	39.4	5.58	0.79	33.7	4.78
.240	3.05	72.8	12.71						
.205	2.38	77.8	11.61						
.215	2.82	80.8	13.10	1.16	33.2	5.39	1.66	47.0	7.71
.220	3.09	80.2	14.05	1.34	34.8	6.09	1.75	45.4	7.96
.280	3.52	66.0	12.57						
.280	3.71	67.8	13.26						
.265	3.04	66.2	11.47	1.32	28.7	4.97	1.72	37.5	6.50
.275	3.49	68.1	12.70						
.260	3.08	63.1	11.85						
.270	3.53	70.4	13.08	1.49	29.7	5.52	2.04	40.7	7.56
.240	3.25	76.8	13.55	1.38	32.8	5.75	1.87	44.0	7.80
.330	4.82	70.8	14.60						
.340	4.96	69.4	14.58	1.98	27.7	5.82	2.98	41.7	8.76
.360	5.42	72.0	15.06	2.61	34.7	7.25	2.81	37.3	7.81
.295	3.84	71.1	13.00	1.81	33.6	6.12	2.03	37.5	6.88
.375	4.08	51.9	10.87	1.90	24.2	5.04	2.18	27.7	5.83
.365	4.76	60.2	13.04						

Subject		Sex	Age years	Height cm.	Weight kg.	Surface area sq.m.
Number	33	F	9/12	70	8.22	0.385
»	34	M	9/12	75	10.80	0.450
»	35	M	9/12	78	11.43	0.480
»	36	F	11/12	68	7.32	0.355
»	37	M	1– 1/12	78	11.60	0.480
»	38	F	1– 2/12	76	10.42	0.450
»	39	F	1– 3/12	79	11.40	0.480
»	40	M	1– 4/12	76	10.15	0.450
»	41	M	1– 6/12	78	11.05	0.470
»	42	M	1– 7/12	85	12.20	0.540
»	43	M	1– 7/12	78	13.55	0.510
»	44	M	2– 1/12	81	9.76	0.460
»	45	F	2– 1/12	86	12.00	0.525
»	46	M	2– 2/12	90	12.66	0.550
»	47	M	2– 2/12	88	13.10	0.540
»	48	F	2– 2/12	82	10.80	0.485
»	49	F	2– 5/12	90	12.85	0.555
»	50	F	2– 6/12	92	13.40	0.580
»	51	M	2– 6/12	89	13.67	0.570
»	52	M	2– 8/12	91	14.80	0.590
»	53	M	2– 9/12	92	12.48	0.555
»	54	M	2–10/12	97	15.25	0.630
»	55	F	3– 3/12	102	13.90	0.630
»	56	M	3–10/12	104	15.11	0.660
»	57	M	4– 0/12	99	16.60	0.660
»	58	M	4– 1/12	104	18.00	0.710
»	59	M	4– 2/12	94	15.00	0.610
»	60	M	5– 0/12	110	16.90	0.720
»	61	M	6– 9/12	118	22.15	0.860
»	62	M	6–10/12	120	23.00	0.880
»	63	F	6–11/12	115	18.50	0.780

Surface area sq.m.	Total Body Water liters	% Body Wt.	l/sq.m.	Extracellular Water liters	% Body Wt.	l/sq.m.	Intracellular Water liters	% Body Wt.	l/sq.m.
0.385	4.36	53.0	11.33						
0.450	6.15	57.0	13.70						
0.480	6.70	58.8	13.96	2.64	23.1	5.50	4.06	35.7	8.46
0.355	4.34	59.3	12.23	1.56	21.4	4.39	2.78	38.0	7.84
0.480	6.60	56.8	13.76	2.93	25.3	6.10	3.67	31.5	7.66
0.450	6.84	65.7	15.20	3.10	29.7	6.88	3.74	36.0	8.32
.480	6.46	56.8	13.46						
.450	5.90	58.2	13.12						
.470				2.66	24.1	5.66			
.540	6.86	56.2	12.71						
.510				3.17	23.4	6.21			
.460	6.59	67.5	14.34						
.525	8.28	69.0	15.76	3.07	25.6	5.84	5.21	43.4	9.92
.550	7.40	58.6	13.46						
.540	8.00	61.1	14.80						
.485	6.97	64.5	14.38	2.70	25.0	5.57	4.27	39.5	8.81
.555	7.96	62.0	14.34	3.54	27.6	6.38	4.42	34.4	7.96
.580	7.54	56.3	13.00	3.41	25.5	5.88	4.13	30.8	7.12
.570	8.84	65.0	15.50	3.01	22.1	5.28	5.83	42.9	10.22
.590				4.47	30.2	7.58			
.555	8.42	67.6	15.31	3.52	28.6	6.40	4.90	39.0	8.91
.630				4.34	29.1	6.90			
.630	10.10	73.3	16.04	2.76	19.9	4.38	7.34	53.4	11.66
.660	9.50	62.8	14.40						
.660	9.15	55.2	13.86						
.710	10.90	60.8	15.35	4.12	22.9	5.80	6.78	37.9	9.55
610	8.83	58.9	14.49						
720	11.64	68.8	16.18	4.48	26.5	6.22	7.16	42.3	9.96
860				5.07	22.9	5.89			
880				4.97	21.6	5.65			
780				4.04	21.8	5.18			

Subject		Sex	Age years	Height cm.	Weight kg.	Surface area sq.m.
Number	65	F	7– 1/12	115	16.80	0.750
»	66	M	7– 4/12	121	20.00	0.830
»	68	M	7– 9/12	126	27.40	0.970
»	69	M	7– 9/12	128	28.00	0.990
»	70	M	8– 0/12	131	27.20	1.00
»	71	M	8– 1/12	119	24.80	0.900
»	72	M	8– 2/12	124	25.30	0.930
»	73	M	8– 2/12	121	21.30	0.860
»	75	M	8– 7/12	128	29.60	1.02
»	76	M	8– 8/12	122	22.00	0.870
»	77	F	8– 9/12	134	25.80	0.990
»	78	M	9– 7/12	147	37.00	1.24
»	80	M	10– 6/12	144	32.90	1.17
»	81	M	10–10/12	132	29.50	1.04
»	82	M	10–10/12	142	38.60	1.29
»	83	M	10–11/12	142	36.70	1.21
»	84	M	11– 0/12	150	41.80	1.32
»	85	F	11– 2/12	157	50.40	1.49
»	86	M	11– 7/12	149	34.40	1.22
»	87	F	11–11/12	163	48.00	1.49
»	88	M	12– 7/12	146	42.70	1.31
»	89	M	12– 7/12	146	35.70	1.22
»	90	M	12–11/12	159	45.00	1.43
»	91	F	13– 0/12	160	43.20	1.41
»	92	F	13– 3/12	148	35.30	1.23
»	93	F	13– 5/12	163	50.40	1.53
»	94	F	13– 6/12	154	43.00	1.37
»	95	F	14– 8/12	157	40.30	1.35
»	96	M	14– 8/12	163	65.40	1.70
»	97	M	15– 6/12	172	55.60	1.65
»	98	M	15– 8/12	175	70.00	1.84

urface area sq.m.	Total Body Water			Extracellular Water			Intracellular Water		
	liters	% Body Wt.	l/sq.m.	liters	% Body Wt.	l/sq.m.	liters	% Body Wt.	l/sq.m.
.750	10.23	60.9	13.75						
.830	11.38	56.9	13.72						
.970	16.20	59.2	16.71						
.990				6.74	25.9	6.81			
.00				5.91	21.7	5.91			
.900				4.85	24.8	5.50			
.930				4.81	19.0	5.18			
.860				4.97	23.3	5.78			
.02				5.22	17.7	5.12			
.870				4.15	18.9	4.77			
.990				5.25	20.3	5.30			
.24				8.12	22.1	6.55			
17				5.75	17.5	4.92			
04				5.24	17.7	5.04			
29	22.4	58.1	17.4						
21	19.0	51.8	15.7						
32				8.03	19.2	6.80			
49	27.1	53.8	18.2						
22				7.35	21.4	6.20			
49	23.9	49.8	16.0						
31	23.4	54.8	17.9						
22	21.0	58.8	17.2						
43	27.3	60.6	19.1						
41	25.2	58.2	17.9						
23	20.1	56.8	16.3						
53	29.7	58.8	19.4						
37	27.6	64.2	20.1	7.52	17.5	5.49	20.1	46.7	14.6
35	23.9	59.5	17.7						
70	38.8	59.2	22.8						
65	35.0	62.9	21.2						
34	44.3	63.2	24.1						

TABLE 2

SUMMARY OF NUMBER AND TYPE OF OBSERVATIONS DIVIDED INTO AGE-GROUPS AND SEX

Measurements of:	Sex	Age-group					TOTAL	
		I 0–11d.	II 11d.–½y.	III ½y.–2y.	IV 2y.–7y.	V 7y.–16y.		
Total body water alone:	M	1	8	4	6	10	29	42
	F	2	2	2	0	7	13	
Total body water and extracellular water:	M	2	5	4	4	0	15	31
	F	3	4	3	5	1	16	
Extracellular water alone:	M	0	0	2	4	12	18	20
	F	0	0	0	1	1	2	
Total number of total body water determinations:	M	3	13	8	10	10	44	73
	F	5	6	5	5	8	29	

Chapter 2.

TOTAL BODY WATER

PREVIOUS WORK

TOTAL BODY WATER IN THE FETUS

The first determination of total body water ever carried out in the human subject was made by v.Bezold in 1857. He found by desiccation that a 5 month old human fetus contained 88 per cent water. It is very interesting to recall that he also demonstrated a gradually decreasing water content in mice during growth, from 87.5 per cent in the embryo, to 83 per cent at birth and 70 per cent in the old animal.

Since then a great number of determinations of the chemical composition of the human fetus have been carried out. All the water determinations were made by desiccation. The results are summarized in table 3, which includes figures from the work of: v.Bezold (1857), Fehling (1877), Michel (1899), Schmitz (1924), Givens and Macy (1933) and Iob and Swanson (1934).

All these observations gave very similar results. The average values gradually decrease from 93.8 per cent during the first month to 75.5 per cent at birth. This decrease is shown in fig. 12 (pag. 50).

TABLE 3

TOTAL BODY WATER IN THE HUMAN FETUS, MEASURED BY DESICCATION, IN PER CENT OF BODY WEIGHT (CALCULATED FROM THE LITERATURE)

Reference	Age in lunar months									
	1	2	3	4	5	6	7	8	9	10
Bezold (1857)					88					
Fehling (1877)	97.5			91.4	90.5	86.3	83.7	82.9		
Michel (1899)		93.8	90.2		87.3	85.1	84.7			
Schmitz (1924)		92.6	90.7	89.1	88.5	86.3				
Givens et al. (1933)	90.0	88.9	89.5	87.5	83.2		83.4			
Iob et al. (1934)		95.4	93.6	88.7	87.5	85.5	83.7	80.9		75.5
Average	93.8	92.7	91.0	89.2	87.5	85.8	83.9	81.9		75.5

TOTAL BODY WATER IN INFANTS

A number of measurements of total body water has been carried out in both premature babies and infants born at full term. Most of these observations have been carried out by desiccation and the results are given in table 4 together with a few measurements in older babies.

This table includes only measurements carried out in "normal" babies; at least they were considered to be in a normal state of nutrition at the time of death. Several other determinations have been made on infants dead from various diseases leading to dystrophy, but these results have not been included. The average values are somewhat lover than those found in the fetus at full term. Prematures have 74.6 per cent water and full-born babies have 71.4 per cent, although large variations are found, from 66 per cent to 80 per cent.

No data on total body water in normal children over one year of age has been found in the literatur.

TABLE 4

TOTAL BODY WATER IN INFANTS, MEASURED BY DESICCATION

Reference	Age	Total body water in per cent of body weight	Mean
Fehling (1877)	premature	73.9	
Brubacher (1890)	"	75.28, 78.01	74.6
Steinitz (1904)	"	71.0	
Bischoff (1863)	newborn	66.4	
Fehling (1877)	"	74.1	
Camerer et al. (1902)	"	71.6, 69.2, 73.0,	
		73.0, 72.0, 72.2	71.4
Klose (1914)	"	65.8	
Job et al. (1934)	"	79.6	
Widdowson et al. (1951)	"	68.8	
Ohlmüller (1882)	2 months	60	60
Brubacher (1890)	7 months	80.75	80.8

TABLE 5

TOTAL BODY WATER IN INFANTS, MEASURED BY THE HEAVY WATER METHOD

Reference	Age	Total body water in per cent of body weight	Mean
Flexner et al. (1947)	1 week	73.2, 73.8 76.8	74.6
Katcher et al. (1953)	1 month	61.6	61.6
	2 months	61.6, 52.1, 72.5, 64.0	62.6
	4 months	57.9, 72.5	65.2
	5 months	70.3	70.3
	7 months	57.0, 61.9, 54.6	57.8
	8 months	59.7	59.7

A few in vivo measurements of total body water in infants have been carried out by the heavy water method by Flexner et al. (1947) and by Katcher et al. (1953). Their results are given in table 5. These average values are similar to those obtained by desiccation, 75 per cent at birth, decreasing to around 60 during the first few months, but great variations are also found here.

RESULTS AND STATISTICAL TREATMENT

The results of 73 determinations of total body water, carried out by the heavy water method, are given in table 1. These results are in agreement with those previously presented, and confirm that total body water, as per cent of body weight, gradually decreases during the first year of life from 75–80 per cent at birth to around 60 per cent at one year of age. From then on total body water varies around 60 per cent, with a group of low values (around 59 per cent) at one year of age and a temporary increase at about two to three years of age (to around 64 per cent).

On the basis of the material presented here a further analysis has been carried out in order to evaluate the changes observed during growth and to investigate the closer relationship between total body water and: body weight, body length or height, body surface area and age. The following abbreviations will be used in the next chapters.

total body water in liter = T; log T = t
body weight in kilogram = W; log W = w

body length or height in centimetre = H; log H = h
surface area in square metre = SA; log SA = sa
age in years = A; log A = a

All difficulties in relating body water to body weight arise from the fact that not all tissues of the body have the same water content. Great variations are found, ranging from cerebrospinal fluid with 99 per cent of water to fat tissue with only 10 per cent. From this it is seen that a given child, weighing 10 kilogram and whose total body water is 6 liters will, if he puts on one kilogram of fat tissue, increase his weight by 10 per cent, but nevertheless his total body water has "decreased" from 60 per cent to 54.6 per cent. Therefore it must be assumed that it is not possible to find any exact relationship between total body water and any one single measurement of the body or a combination of several measurements in terms of body indices. Similar difficulties have also been encountered in attempts to compare such functions as basal metabolism, kidney function and heart volume from one individual to another, or in calculating "normal values" for such functions.

In spite of these difficulties it is, however, of interest to investigate the relationship between: T and W, H, SA and A, since similar analyses not have been carried out previously and might throw new light upon the relationship between total body water and body size. Valuable information about changes in body water compartments during growth should also be gained when the same calculations are carried out for E and I.

The following 5 possibilities will be considered; total body water related to:
1) the age of the subject,
2) both weight and height,
3) the body surface area as calculated from the Du Bois formula and monogram,
4) the weight alone and
5) the height alone.

1) TOTAL BODY WATER RELATED TO AGE

The measured values of T, W and H have been plotted against A as seen in figure 2, 3 and 4. A double logarithmic scale has been used in order to make clear the changes found during the first months of life.

This relationship may be expressed as:

(1) $$t = \alpha_1 + \beta_1 (a - \bar{a}) + u_1$$
(2) $$w = \alpha_2 + \beta_2 (a - \bar{a}) + u_2$$
(3) $$h = \alpha_3 + \beta_3 (a - \bar{a}) + u_3$$

where α_1, α_2 and α_3 are constants representing the level of the regression lines within each age group, and β_1, β_2 and β_3 (the coefficients of regression) are

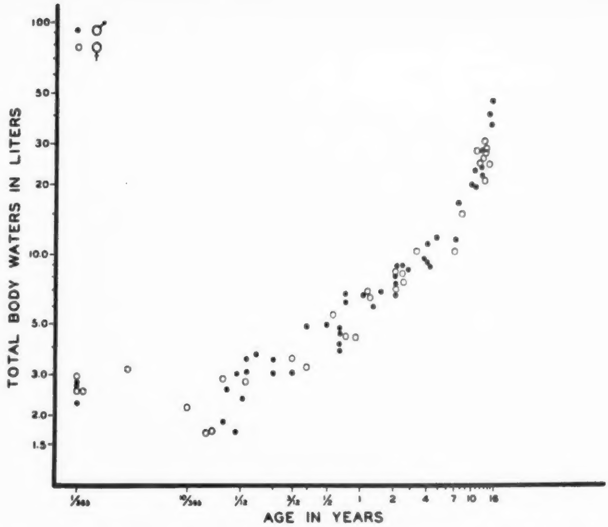

Fig. 2. The increase of total body water during growth, from birth to 16 years of age, presented on a double logarithmic scale.

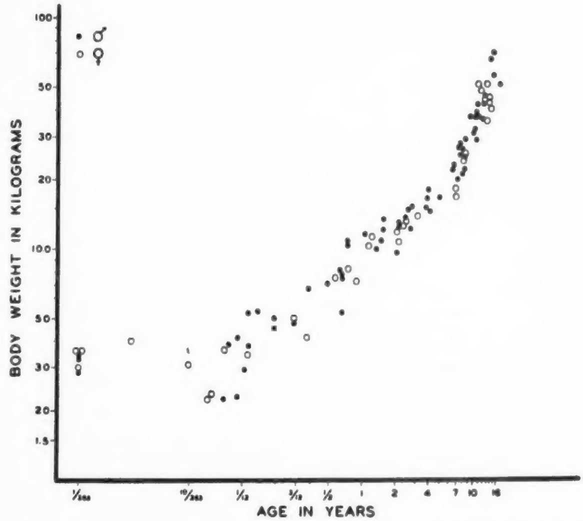

Fig. 3. The increase of body weight during growth, from birth to 16 years of age, presented on a double logarithmic scale.

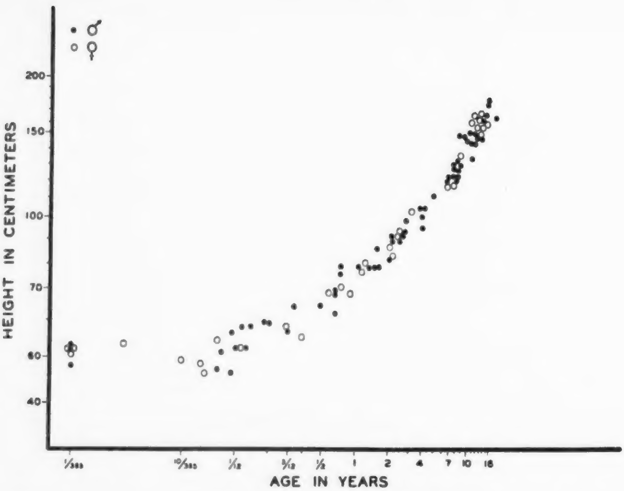

Fig. 4. The increase of body length or height during growth, from birth to 16 years of age, presented on a double logarithmic scale.

constants representing the slopes of the regression lines; $\bar{a}$ is the average of the logarithm of the ages in each group and the quantities u_1, u_2 and u_3 are the random deviations from the regression lines.

Estimates of α_1, α_2 and α_3 have been calculated from the material by the method of least squares (see e.g. Hald, 1952). These estimates are the means: $\bar{t}$, $\bar{w}$ and $\bar{h}$ and the calculated values are given in table 6, where the values of $\bar{a}$ also are found.

The estimates of the slopes: β_1, β_2 and β_3 are denoted by b_1, b_2 and b_3. These values are given in table 7 together with their standard errors. It is seen here that the slopes in group II, III and IV are almost equal in contrast to the much greater slope observed in group V.

The charts illustrate the changes during growth and it is seen in all 3 figures that no consistent changes are found during the first 10 days of life. After this time a gradual increase is found in such a fashion, that the "curve" is bent upwards, but this part may nevertheless be described by 2 straight lines: one in the interval from 11 days to 7 years, and another with a much greater slope from 7 to 16 years of life. It is also apparent that the growth of the 2 sexes proceeds in a similar fashion, for which reason no differentiation between the sexes will be made in the treatment of the material.

The changes found during the first 10 days of life have not been subjected to a complete statistical treatment, since other factors than growth are at play, and the material is not fitted to give exact information about the highly

important changes in water metabolism at the beginning of independent life. Such knowledge would better be obtained from repeated measurements in a few babies during the first 2 weeks of life. This project is planned for future investigation.

The remaining part of the material has been divided into 4 groups. First the subjects over 7 years of age have been taken as one group, and the rest, ranging from 11 days to 7 years, has been divided into 3 groups. This gives 4 groups of almost equal size. The number of observations in each group are given in table 2 and 6.

It is then assumed that the relationship between: t, w, h and a is linear within the age groups II–V, apart from random variations.

From the found relationship between total body water and age, the water content of a given child may be calculated from its age as:

$$t_{calc} = \bar{t} + b_1 (a - \bar{a}) \qquad (4)$$

with $\bar{t}$, $\bar{a}$ and b_1 taken from tables 6 and 7 for each age group.

TABLE 6

AVERAGE OF THE LOGARITHMS OF: T, W, H AND A AND THE ANTILOGARITHMS

	Age-group				
Number of observations	I	II	III	IV	V
	8	19	13	15	18
average of log T : $\bar{t}$	0.422	0.458	0.736	0.933	1.368
antilog $\bar{t}$	2.63	2.87	5.45	8.57	23.32
average of log W : $\bar{w}$	0.530	0.600	0.962	1.133	1.604
antilog $\bar{w}$	3.39	3.98	9.16	13.57	40.16
average of log H : $\bar{h}$	1.709	1.734	1.863	1.970	2.175
antilog $\bar{h}$	51.2	54.2	73.0	93.2	149.5
average of log A : $\bar{a}$	0.185	1.627	2.506	3.016	3.630
antilog $\bar{a}$ (years and days)	0y 1½ d	0y 43d	2y 321d	2y 306d	11y 250d

TABLE 7

COEFFICIENTS OF REGRESSION AND THEIR STANDARD ERRORS (S. E.)

Regression of		Age-group			
		II	III	IV	V
t versus a	b_1	0.351	0.420	0.447	1.382
	(S. E.)	(0.064)	(0.157)	(0.076)	(0.164)
w versus a	b_2	0.388	0.508	0.474	1.324
	(S. E.)	(0.071)	(0.169)	(0.074)	(0.170)
h versus a	b_3	0.111	0.207	0.267	0.447
	(S. E.)	(0.019)	(0.051)	(0.036)	(0.042)

The difference between the calculated and the actual value of t is:

(5) $$t - t_{calc} = (\alpha_1 - \bar{t}) + (\beta_1 - b_1)(a - \bar{a}) + u_1$$

The main part of this difference is the random component u_1 representing the individual deviations from the true regression lines. The remaining part represents the difference between the true and the estimated regression line, but since $\bar{t}$ and b_1 (that are estimates of the true values: α_1 and β_1) are based upon about 16 observations (13 – 19 per age group) the deviation due to these two components will be small compared to the variation of u_1. The average standard deviation of u_1 (within groups II to V) is 0.0718 corresponding to a relative standard deviation of 18.0 % of the calculated total body water.

2) TOTAL BODY WATER RELATED TO WEIGHT AND HEIGHT

The above calculation of t has been based upon the age of the subject alone (formula 1). It is, however, evident that great variations are found among normal subjects of the same age and by analysis it is found, that the random deviations: u_1, u_2 and u_3 are positively correlated, which simply means that children whose total body water exceeds the average for their age, as rule will be heavier and taller than the average, and vice versa.

The coefficients of correlation between: u_1/u_2, u_1/u_3 and u_2/u_3 are given in table 8. These values are all positive varying from 0.52 to 0.97, and it

should therefore be possible to obtain a better estimate of total body water from weight and height rather than from the age alone.

This is in agreement with the previous statement that the total body water is not only determined by the age and weight of the subject but also by the body build, which is reflected in the relationship between the weight and the height of the child.

In order to find the best linear estimate of t based upon observations of weight and height an analysis of the regression of t on w and h has been carried out (see e. g. Hald, 1952). If t is assumed to be linearly related to w and h except for random variations, we have:

$$t = \alpha_1 + \beta_w (w - \overline{w}) + \beta_h (h - \overline{h}) + y \tag{6}$$

where α_1, β_w and β_h are unknown constants and y is a random variable, that is varying around zero with the standard deviation σ.

The estimate of α_1 is $\overline{t}$ (table 6 and 9) and the estimate of σ is s. The values of s found within each of the groups II to V are not significantly different, and the standard deviation is therefore regarded as independent of age. The average value of s common for the 4 age groups is calculated as 0.0333, determined by 59 degrees of freedom.

The estimates og β_w and β_h are denoted by b_w and b_h (table 9). These values varies somewhat but it must be noted that the low value of b_w in group IV corresponds to a high value of b_h. This is caused by the close correlation between b_w and b_h, which will be discussed later. When the 4

TABLE 8

COEFFICIENTS OF CORRELATION BETWEEN THE DEVIATIONS u_1, u_2, u_3

	Age-group			
	II	III	IV	V
u_1/u_2	0.942	0.852	0.529	0.925
u_1/u_3	0.875	0.832	0.674	0.683
u_2/u_3	0.917	0.966	0.518	0.767

TABLE 9

THE CALCULATED ESTIMATES: $\bar{t}$, b_w, b_h, AND THE STANDARD DEVIATION: s

	Age-group				Average
	II	III	IV	V	
$\bar{t}$	0.458	0.736	0.933	1.368	
b_w	0.794	0.687	0.267	0.939	0.790
b_h	0.312	0.351	1.189	0.242	0.425
s	0.0297	0.0418	0.0275	0.0305	0.0333

paired values of b_w and b_h are compared no significant difference is found and average values of b_w and b_h have been calculated (table 9).

For a given child t may then be calculated by the formula:

$$(7) \qquad t_{calc} = \bar{t} + 0.790\ (w - \bar{w}) + 0.425\ (h - \bar{h})$$

or

$$(8) \quad t_{calc} = (\bar{t} - 0.790 \cdot \bar{w} - 0.425 \cdot \bar{h}) + 0.790 \cdot w + 0.425 \cdot h$$

The three figures within the brackets have to be calculated separately for each group from the values of $\bar{t}$, $\bar{w}$, and $\bar{h}$ found in table 6.

Total body water is then calculated as:

$$(9) \qquad T = C_A \cdot W^{0.790} \cdot H^{0.425}$$

where C_A is the antilogarithm of $(\bar{t} - 0.790 \cdot \bar{w} - 0.425 \cdot \bar{h})$ that calculated within each age group is: 0.177, 0.153, 0.195 and 0.150.

The difference between the calculated and the actual t is:

$$(10) \quad t - t_{calc} = \alpha_1 - \bar{t} + (\beta_w - b_w) \cdot (w - \bar{w}) + \beta_h - b_h) \cdot (h - \bar{h}) + y$$

If w and h does not deviate too much from the average value of $\bar{w}$ and $\bar{h}$ within the given age group the standard deviation of $(t - t_{calc})$ will be approximately

mately equal to the standard deviation of y, which in this material is found to be 0.0333, corresponding to a relative standard deviation of 7.9 % of the calculated T.

T may also be calculated from a formula where the constants are common for the groups II – V. This formula is:

$$(11) \qquad T = 0.153 \cdot W^{0.706} \cdot H^{0.483}$$

The relative standard deviation of T calculated from this formula is 8.8 % (of T) which is an increase of 10 per cent of the 7.9 % found from formula (9). By this calculation of T a systematic error is introduced for children whose weight and height deviate most from the mean of the material.

Since the use of formula (9) and (11) is rather cumbersome and only gives a fair degree of accuracy, it is worth while finding an easier calculable estimate for which the standard deviation is not too much greater.

TOTAL BODY WATER RELATED TO: 3) BODY SURFACE AREA, 4) WEIGHT AND 5) HEIGHT

The surface area of the body (SA) may be calculated from the formula of Du Bois (in square metre when H is in cm):

$$(12) \qquad SA = \frac{71.84}{10^4} \cdot W^{0.425} \cdot H^{0.725}$$

which is the same as:

$$(13) \qquad sa = (0.8563 - 3) + 0.425 \cdot w + 0.725 \cdot h$$

The relationship between t and sa may be written in a similar fashion as formula (1):

$$(14) \qquad t = \alpha_1 + \beta_{sa} (sa - \overline{sa}) + y$$

where α_1 and β_{sa} are constants and $\overline{sa}$ is the average of the logarithm of the surface areas within each group and y the random deviation from the regression line.

From formula (13) and (14) it is seen that:

$$(15) \quad t = \alpha_1 + 0.425 \cdot \beta_{sa} (w - \overline{w}) + 0.725 \cdot \beta_{sa} (h - \overline{h}) + y$$

This is the same as formula (6) where β_w is $0.425 \cdot \beta_{sa}$ and β_h is $0.725 \cdot \beta_{sa}$.

The difference between the two possibilities is then that the ratio

$\frac{\beta_w}{\beta_h}$ has been made $= \frac{0.425}{0.725}$

When total body water is related to either body weight or height alone, these relationships may also be derived from formula (6) by taking either $\beta_h = 0$ or $\beta_w = 0$. In these cases we have:

$$t = \alpha_1 + \beta_w (w - \bar{w}) + y \tag{16}$$
$$t = \alpha_1 + \beta_h (h - \bar{h}) + y \tag{17}$$

As a special possibility of formula (16) one may choose $\beta_w = 1$ in which case total body water is expressed as per cent of body weight.

Since the weight and the height are closely correlated, considerable changes may be made in the choice of β_w and β_h without seriously effecting the fit and

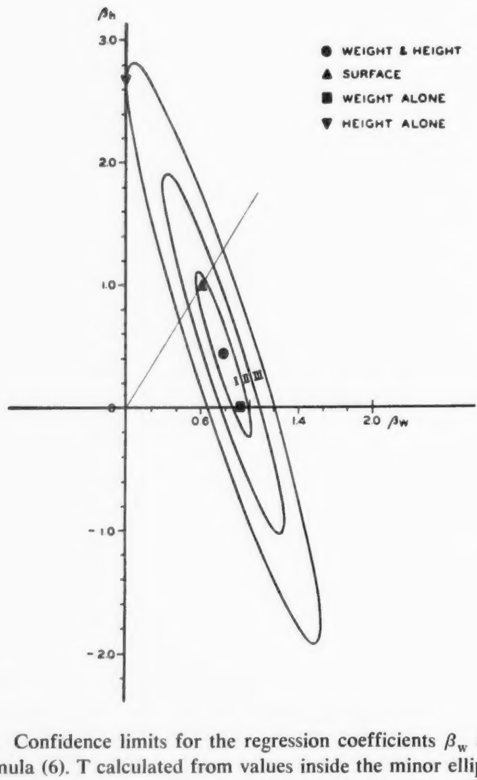

Fig. 5. Confidence limits for the regression coefficients β_w and β_h of formula (6). T calculated from values inside the minor ellipses (I) are acceptable, whereas values outside (I) but inside (II) or (III) will increase the standard deviation by at most 20 or 50 per cent respectively. For further explanation see the text.

it is possible within each group to define the limits of variation for the combinations of β_w and β_h. This is shown graphically in figure 5 where a coordinate system has been constructed with β_w as abcissa and β_h as ordinate. Then each point in the coordinate system corresponds to a pair of β_w and β_h. Three ellipses have been constructed with a common center which corresponds to the previously found optimal values of $\beta_w = 0.790$ and $\beta_h = 0.425$. The ellipses have been constructed in such a fashion that the interior of the smallest of the ellipses (I) forms the 95 per cent confidence region, which means that a point within this region corresponds to an acceptable combination of β_w and β_h, whereas values outside this ellipse will increase the estimate of the standard deviation s. The extent of this error may also be judged from the figure, where ellipses (II) and (III) correspond to paired values of β_w and β_h that will increase the standard error by at most 20 per cent and 50 per cent respectively.

The situations corresponding to formula (14), (16) and (17) as discussed above, have also been marked on the figure.

The use of the surface formula corresponds to a ratio $\beta_w/\beta_h = 0.425/0.725$ which relationship is shown by the straight line in fig. 5. This line will intersect the major-axis of the ellipses at (▲) which is just inside (I), which means that the relationship between total body water and surface area is acceptable. The standard deviation has in this case increased from 7.9 % to 8.2 %.

The major-axis will intersect the abscissa at 0.922 (■) corresponding to $\beta_h = 0$ or calculation of t from the weight alone. Weight to the 0.9 power will therefore also give an acceptable fit (s is 8.0 %), whereas total body water as per cent of the weight or $\beta_w = 1.0$ is just outside region (I), (s is 8.1 %).

In contrast to this the calculation of T from height alone corresponds to $\beta_w = 0$ and $\beta_h = 2.658$. This is indicated on the figure by the mark (▼) which is just in the periphery of (III) and accordingly the standard error in this case is increased by 50 per cent to 12 %.

The five different combinations of β_w and β_h are summarized in table 10 together with the relative standard deviation obtained by each pair af values.

The best correlation is obtained when total body water is calculated from both weight and height, giving a relative standard deviation of 7.9 %. This is however only slightly better than the relative standard deviation obtained by the more simple correlations: weight alone: 8.0 %; per cent of the weight: 8.1 %, or from the surface area: 8.2 %; whereas a considerably higher standard deviation is found when T is calculated from the height alone: 12 %.

The simplest correlation is to calculate total body water as per cent of the body weight within the age groups and this is also the only one suited for practical clinical work. As seen above the results obtained in this way are almost as good as those obtained by the more elaborate methods. Therefore, to conclude, total body water is given as per cent body weight in table 11 for

TABLE 10

THE RELATIVE STANDARD DEVIATION OBTAINED WHEN T IS CALCULATED FROM DIFFERENT CORRELATIONS

Total body water related to:	β_w	β_h	Relative standard deviation
weight and height	0.790	0.425	7.9 %
surface area	0.425	0.725	8.2 %
weight	0.922	0	8.0 %
per cent of weight	1.000	0	8.1 %
height	0	2.658	12.0 %

TABLE 11

T IN PER CENT OF BODY WEIGHT AND IN LITERS PER SQUARE METER SURFACE AREA, AND THE STANDARD ERROR (S. E.)

	Age-group				
	I	II	III	IV	V
T/W in % (S. E.)	77.6 (2.2)	72.2 (1.3)	59.5 (1.3)	63.1 (1.3)	58.4 (1.1)
T/SA in 1/sq.m (S. E.)	12.6 (0.66)	12.3 (0.41)	13.2 (0.54)	14.7 (0.56)	17.9 (0.62)

each age group including group I. In figure 6 this relationship is presented on a semilogarithmic sale, whereby the changes during the first year of life are shown more clearly.

A continuous fall in body water during the first year of life is seen on figure 6. The fall from group I to II and from group II to III is significant (the differences being 2.1 and 6.9 times the standard error). Then a small increase is found from group III to IV which is hardly significant (only 1.96

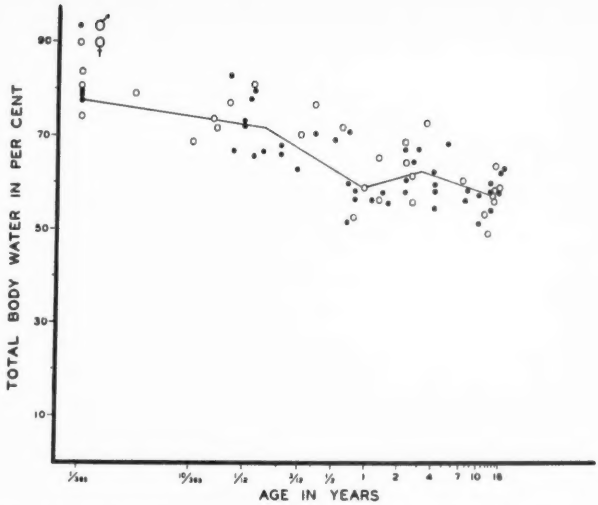

Fig. 6. Total body water in per cent of body weight related to age on a semilogarithmic scale. The curve is drawn through the mean values of the age-groups I to V (table 11).

times the standard error) and from group IV to V a small, but significant, decrease is again observed (2.8 times the standard error).

A closer examination, however, of figure 6 reveals that the individual variations within each group are rather large, yet a group of low values, less than 60 per cent, are found around one year of age. This may be related to the fact that children at this age, just when they begin to walk and develop their muscles, are very fat. Stuart and Sobel (1946) who measured the thickness of subcutaneous tissue in children as judged from the antero-posterior roentgenogram of the leg came to a similar conclusion: that relatively the highest values were found in children of about one year of age.

CHANGES IN TOTAL BODY WATER DURING GROWTH

Several investigators have shown that the relative amount of total body water decreases gradually during the life span. This has been shown to be the case in both pre- and postnatal life and has been found in both the human subject and in animals.

These observations have been reviewed among others by: Aron (1927), Shohl (1939), Needham (1942) and Lowry and Hastings (1942). The human

data treated in these papers have been obtained by desiccation and have mainly included observations of fetuses and young children, but recent in vivo experiments including all age groups have given the same result (Edelman et al., 1952).

Huxley (1932), who studied the problems of relative growth, introduced the term a "constant differential growth ratio" (k) by which he described the relationship between the growth of an organ or a limb and that of the whole body.

The formula for this ratio is: $y = b \cdot x^k$ where y is the part of the body and x is the whole body (measured in the same units) and b is the proportionality constant.

This ratio has been used by Needham (1942) to describe "chemical growth", although he preferred the term "heterauxesis" for this type of "differential growth ratio". He compared the dry weight to the wet weight of a number of different animals during development and found that within any one group there is a marked similarity of k, that is to say, they get drier at the same rate. However, variations were found between different species. The value of k in mammals, including man, is 1.23, which is higher than the average value found in birds (1.19), reptiles (1.15), amphibias (1.09), insects (1.04) and in teleostean fishes (1.00).

This shows that mammals get drier during growth at a faster rate than other species and that all animals get drier, except the fish whose water content remains constant.

It has been suggested that there may be a relationship between the absence of progressive dehydration with age in teleostean fishes, such as the carp, and the possible absence of death from senility (Needham, 1942). The evidence is, however, too slender to draw any conclusions.

The relationship between water and dry substance in the human fetus was studied by Hamilton (1936) on the basis of the date obtained by Iob and Swanson (1934) by desiccation. He demonstrated a constant differential growth ratio, but was unable to compare these observations to similar data in children and adults, due to lack of observations of this kind.

The same problem was later taken up by Forbes (1952) who compared the total body water determinations made by: Fehling (1877), Schmitz (1924), Iob and Swanson (1934), Flexner et al. (1947), Schloerb et al. (1950) and Friis-Hansen et al. (1951). He concluded that, during early fetal life (up to 1 kg of body weight), total body water on a per kilogram basis changed very little, but from then on a gradual drying out took place during the rest of the life span. He found that the regression line of the latter group of data fits these quite well, with a standard deviation of about 10 %. He concluded, that from midfetal life to the period of young adulthood, chemical growth, as regards water, potassium and sodium, proceeds in a manner which conforms to the differential growth equation.

In order to illustrate these changes total body water has been plotted against body weight on a double logarithmic scale, from early fetal life (about 1 g) to the adult subject (80 kg), as seen in figure 7. This graph includes observations of: v.Bezold (1857), Fehling (1877), Givens et al. (1933), Iob et al. (1934), Edelman et al. (1952) and the present data. The straight line indicates the 1/1 relationship. A closer examination of the figure reveals that the plot is a straight line up to values corresponding to a body weight of 3 to 10 kg, during which period a break in the curve takes place, whereafter a straight line again is found. This corresponds to the changes seen in figure 6 and 12, where it is seen that the greater part of the postnatal decrease in total body water takes place during the first year of life.

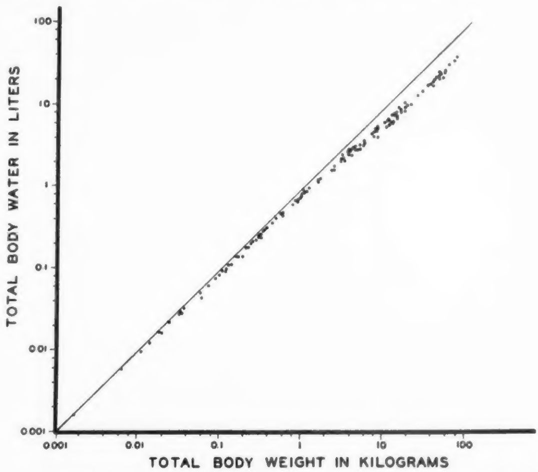

Fig. 7. The relationship between total body water in liters and body weight in kilograms on a double logarithmic scale, based upon observations of: v.Bezold (1857), Fehling (1877), Schmitz (1924), Givens et al. (1933), Iob et al. (1934), Edelman et al. (1952) and the present observations.

A similar change was observed in the rat by Hamilton and Dewar (1938) who demonstrated that a "drying out" took place during the neonatal period. If, therefore one concludes, as Forbes (1952) did, that chemical growth is a regular and systematic process throughout most of the span of human life, it is necessary to add that regarding body water, a definite break of the smooth growth curve takes place during the first year of life, and that total body water does not conform strictly to a constant differential growth ratio. This "law", therefore, as many other similar "laws", can only be advanced as a "law" if one does not claim too rigid a fit to the phenomena it describes.

Chapter 3.

EXTRACELLULAR WATER

PREVIOUS WORK

EXTRACELLULAR WATER IN THE HUMAN FETUS

Only a few calculations of the amount of extracellular fluid in the human fetus have been carried out. Harrison, Darrow and Yannet (1936) have estimated the extracellular fluid volume from the total chloride content, making the assumption that the extracellular concentration of chloride is 120 mmol. per liter. Their calculations were based upon the data of Iob and Swanson (1934). Similar calculations have been carried out by Stearns (1939), who arrived at almost the same figures. The results are given in table 12. The very high value of 62 per cent, found at 5 lunar months of age, is more than two thirds of the total amount of water at that period. At birth the extracellular water has decreased to 43 per cent, which is still more than half the total.

These average values are shown in figure 12 (pag. 50).

TABLE 12

EXTRACELLULAR WATER IN THE HUMAN FETUS, IN PER CENT OF BODY WEIGHT

Reference	Age in lunar months			
	5	6	8	10
Harrison et al. (1936)	62	60	53	43
Stearns (1939)		58	51	43
Average	62	59	52	43

EXTRACELLULAR WATER IN INFANTS AND CHILDREN

Several authors have measured the extracellular water volume in children. The results have been collected in table 13. Most of these observations have been carried out by the thiocyanate method, giving average values of 37.8 per cent during the first half year of life and 29 per cent around puberty.

TABLE 13

EXTRACELLULAR FLUID VOLUME IN CHILDREEN IN PER CENT OF BODY WEIGHT. MEASURED BY DIFFERENT METHODS (CALCULATED FROM THE LITERATURE)

Reference	Age in years					Method
	0–½	½–1	1–2	2–5	5–15	
Schultz et al. (1940)					25.5	thiocyanate
Morse et al. (1947)				28.8	29.0	–
Schneegans (1949)	37	28				–
Fellers et al. (1949)	41.2	35.0			32.2	–
Hallman et al. (1950)	41	36				–
Ely et al. (1952)	39.3	32.9	31.9	29.9	29.1	–
Parsaro et al. (1953)	30.7					–
Average	37.8	32.9	31.9	29.4	29.0	thiocyanate
Flexner et al. (1947)	43.5					Na24
Fellers et al. (1949)	42.6	33.0			35.6	–
Perley et al. (1951)	35.2				30.2	–
Calcagno et al. (1951)	33.4		36.1			inulin
	34.4					sodium ferro-cyanide
Friis-Hansen et al. (1952)					16	inulin
Katcher et al. (1953)	27.3	25.3				–

These values are somewhat lower than those found by radioactive sodium and on the other hand somewhat larger than the corresponding inulin volume.

Most of these investigators have been able to demonstrate a gradual decrease of the extracellular fluid volume during growth, when expressed as per cent of body weight. When measured by the thiocyanate method, this decrease amounts to about 10 to 15 per cent, which is less tran the observed decrease of 20 to 25 per cent found by the thiosulfate method. This difference will be discussed later. Ely and Sutow (1952), who at the same time measured blood volume, were able to demonstrate in their subjects that interstitial fluid showed the same decrease as the extracellular fluid, whereas the blood volume remained practically constant.

Extracellular water (E) has been measured in 51 subjects: 18 girls and 33 boys.

The results are given in table 1. The material has been divided into the same age groups as the measurements of total body water.

The extracellular water volume has been plotted against age on a double logarithmic scale as seen in figure 8. Like total body water, no consistent change has been observed during the first 10 days of life, but thereafter a gradual increase is found. No difference between boys and girls has been noted.

The relationships between E and weight (W), height (H) and surface area (SA) have been investigated in a similar fashion to the analysis of total body water described in the previous chapter.

The averages of the logarithms of E, W, H and A have been calculated, the results are given in table 14.

The relationship between E and W and H is found to be:

$$E = C_E \cdot W^{0.672} \cdot H^{0.163}$$

where C_E is a constant which within the age groups II – V is: 0.279, 0.270, 0.285 and 0.274. The observed standard deviation of E from this relationship has been calculated as 15.2 %.

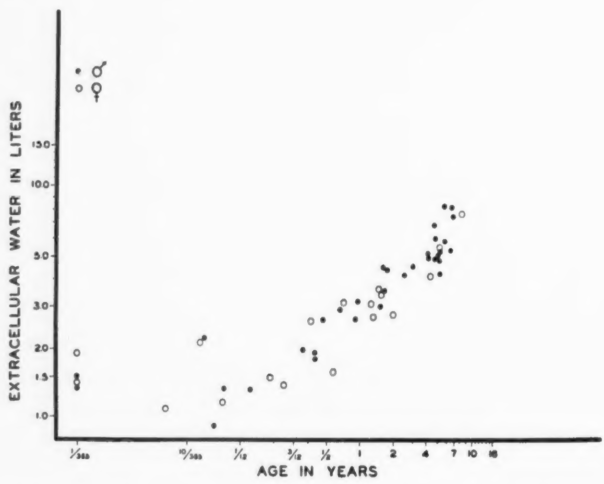

Fig. 8. The increase of extracellular water in liters during growth, from birth to 16 years of age, presented on a double logarithmic scale.

TABLE 14

AVERAGE OF THE LOGARITHMS OF: E, W, H AND A
AND THE ANTILOGARITHMS

Number of observations	Age-group				
	I	II	III	IV	V
	5	9	9	14	14
average of log E : $\bar{e}$	0.153	0.140	0.384	0.573	0.768
antilog $\bar{e}$	1.42	1.38	2.42	3.74	5.87
average of log W : $\bar{w}$	0.535	0.611	0.965	1.181	1.470
antilog $\bar{w}$	3.42	4.08	9.23	15.2	29.5
average of log H : $\bar{h}$	1.712	1.735	1.861	1.993	2.127
antilog $\bar{h}$	51.5	54.3	72.6	98.4	133.9
average of log A : $\bar{a}$	0.200	1.697	2.526	3.091	3.528
antilog $\bar{a}$ (years and days)	15d	50d	336d	3y 137d	9y 90d

When E was calculated as per cent of W within the age groups the same relative standard deviation 15.2 %, was found.

This standard deviation is almost twice the standard deviation of T. It is debatable whether the high standard deviation of E represents physioligical variations or only reflects a greater analytical error in the measurement of E, especially in the low age groups, where the highest deviation is found.

Reproducibility of the measurement of extracellular water by the thiosulfate method has been shown by duplicate determinations. In six healthy male adults studied on two occasions at short time intervals, the average difference between the two measurements was 0.8 % (Cardozo and Edelman, 1952). Similarly in three children an average difference of 1.2 % was found (Friis-Hansen, 1954). These findings seem to indicate that the high standard deviation of E cannot be explained by inaccuracy of the measurements.

When E is related to SA, an exponent is found, which is not significally dif-

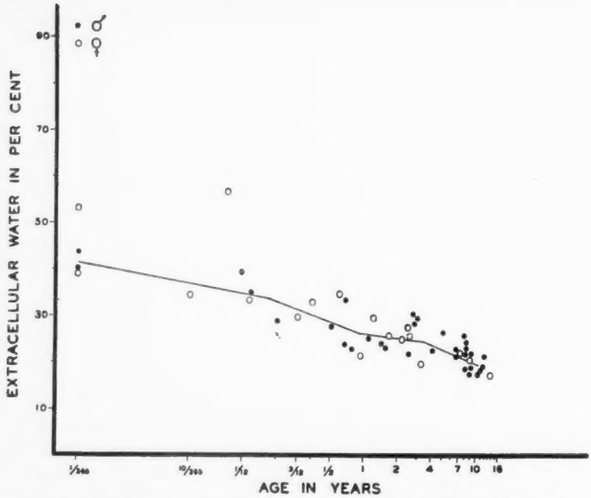

Fig. 9. Extracellular water in per cent of body weight related to age on a semilogarithmic scale. The curve is drawn through the average values of the age-groups I to V (table 15).

ferent from 1.00 and E may thus be expressed in liters per square meter of SA. The standard deviation of this relationship is 15.3 %.

The values of E calculated from W and SA are given in table 15 together with the standard errors within each age group, and in figure 9 E in per cent of W has been plotted against age on a semilogarithmic scale. The highest values are found in the neonatal period where values above 50 % have been found; a gradual decrease then follows, most pronounced during the first six months of life, but continuing throughout childhood. Even during puberty, the values are slightly higher than the normal value in the adult male, where the thiosulfate volume has been reported to be 16.6 %. The magnitude of the decrease of E throughout the age groups I – V is: 2.4, 3.5, 0.91 and 3.7 times the standard error.

It is interesting to see that E expressed as liters per square meter of body surface area, remains constant during growth. A small, but hardly significant, fall from 6.74 to 5.83 is observed from age group I to II (1.65 times the standard error). This remarkable constancy is difficult to explain even though it may to some extent be related to the fact that, at least in children, a greather part of the total extracellular fluid is found in the skin and subcutaneous tissue than in any other single organ.

When the figures of table 13 are compared to the results given here, it is noted that the thiocyanate volumes during the first half year of life are

TABLE 15

E IN PER CENT OF BODY WEIGHT AND IN LITERS PER SQUARE METER SURFACE AREA AND THE STANDARD ERROR (S. E.)

	Age-group				
	I	II	III	IV	V
E/~~SA~~W in % (S. E.)	41.6 (2.8)	33.7 (1.7)	26.2 (1.3)	24.7 (1.0)	19.9 (0.8)
E/SA in l/sq.m. (S. E.)	6.74 (0.46)	5.83 (0.30)	5.86 (0.30)	5.89 (0.24)	5.57 (0.23)

equal to the thiosulfate volume, whereas the thiocyanate volume at 5 to 15 years is 10 per cent higher than the corresponding thiosulfate volume. In adults the thiocyanate volume is also about 10 per cent higher than the extracellular fluid volume as estimated by thiosulfate and it is difficult to explain why the volumes are of equal size during the first half year.

The values obtained by Na-24, are even higher, whereas most of the inulin volumes are lower than the corresponding thiosulfate values.

EXTRACELLULAR FLUID AND KIDNEY FUNCTION

As described previously (Friis-Hansen, 1954), the extracellular fluid volume has been measured by determination of the disappearance curve of thiosulfate in blood after intravenous injection. The slope of this curve is the resultant of both renal and extrarenal elimination and is furthermore determined by the relationship between the rate of removal and the volume of extracellular fluid.

Thiosulfate clearance has been widely used as a measure of renal function (glomerular filtration rate), and in spite of the fact that only between two-thirds and three-quarters of the amount injected is rescovered in the urine, a fair estimate of the thiosulfate clearance may be obtained from the slope by expressing this as per cent per minute (Newman, Gilman and Philips, 1946). In adults values between 0.6 and 1.4 per cent were obtained. This has also been done in the present investigation and the results are given in table 16

TABLE 16

THIOSULPHATE CLEARANCE, CALCULATED FROM THE SLOPE OF THE DISAPPEARANCE CURVE, EXPRESSED AS PER CENT PER MINUTE

Age	Number of observations	Mean	Range
0– 1 day	4	0.25	0.18–0.30
1–30 days	4	1.10	0.70–2.00
1– 3 months	3	1.50	1.06–2.32
3– 6 months	3	1.39	1.18–1.70
6–12 months	5	1.55	1.10–1.98
1– 2 years	4	1.53	1.37–2.30
2– 3 years	8	2.13	1.34–2.46
3– 5 years	2	1.98	1.51–2.44
5–10 years	12	1.94	1.40–2.48
10–15 years	4	1.99	1.68–2.24

as average values in different age groups. Thiosulfate clearance was found to be very low in newborn babies, but the values are rapidly increasing during the first month of life at which time adult values are reached. Even higher values are found later in childhood. This is in contrast to the observation that when compared on the basis of surface area, kidney function in infants and children up to one to two years of age is lower than in adults. McCance and Widdowson (1952), who have done extensive studies in this particular field, have recently stated their doubts, as to whether surface area is the correct physiological basis on which to compare renal function in infants and adults. These authors have advocated the use of total body water as a more correct basis of comparison, since such substances as urea are distributed evenly throughout the total body water.

When urea clearance and glomerula filtration rate are calculated per 42 liters of body water, adult values are reached during the first weeks of life, and even higher values are then found early in chilhood. This important question has not yet been settled, but since extracellular fluid is the medium, so to speak, with which the kidneys primarily work, it may be more "physiological" to compare kidney function to the volume of extracellular fluid.

The parallel changes in surface area and extracellular fluid volume which have been shown to occur during growth, may therefore explain why a close relationship has been found between renal function and surface area. This relationship may be only an indirect one caused by the interdependence between renal function and extracellular fluid volume and between this volume and surface area.

Chapter 4.

INTRACELLULAR WATER

PREVIOUS WORK

INTRACELLULAR WATER IN THE HUMAN FETUS

The intracellular water in the fetus has been calculated by Harrison, Darrow and Yannet (1936). They calculated the extracellular water from the amount of chloride present and the intracellular water by subtracting the extracellular from the total water content obtained by desiccation. These calculations were based upon the observations of Iob and Swanson (1934). Stearns (1939) arrived at a very similar result by calculating the intracellular water from the total amount of potassium in the fetus. The results are given in table 17. At 5 lunar months the intracellular water only amounts to 25 per cent of body weight, which is less than one third of the total and less than half the extracellular water. The 32 per cent found at birth is only slightly less than the adult value of 35 to 45 per cent. The gradual increase of intracellular water during fetal life is shown in figure 12, where the graph represents the average values of table 17.

TABLE 17

INTRACELLULAR WATER IN THE HUMAN FETUS, IN PER CENT OF BODY WEIGHT

Reference	Age in lunar months			
	5	6	8	10
Harrison et al. (1936)	25	26	29	32
Stearns (1939)		28	29	31
Average	25	27	29	32

INTRACELLULAR WATER IN INFANTS

Only a few estimations of intracellular fluid in infants are recorded. Katcher et al. (1953) measured the deuterium and the inulin volumes of dilution in 9 normal infants and estimated the intracellular water as the non-inulin body

water. They found an average value of 35.0 per cent ranging from 21.1 to 45.9 per cent, with no consistent change in relation to age.

RESULTS AND STATISTICAL TREATMENT

The volume of intracellular water, I, has been calculated in the subjects where both total and extracellular water were measured at the same time, as: I = T − E. This has been done in 31 subjects, 16 girls and 15 boys. The results are given in table 1, and the number of observations in the different age groups are given in table 2.

I has also been plotted against A on a double logarithmic scale in figure 10. Again, no difference is found between the sexes, and I remains unchanged during the first ten days of life and then increases with age.

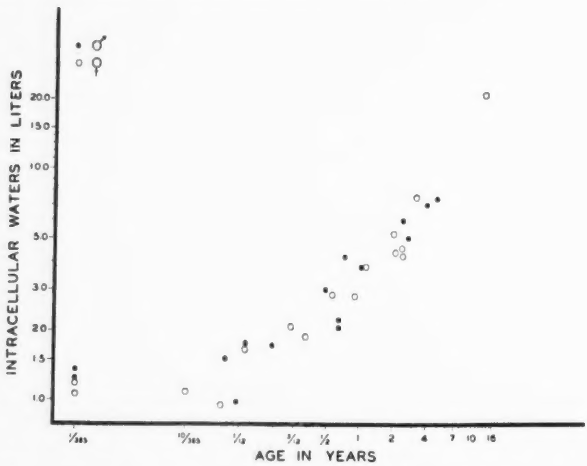

Fig. 10. The increase of intracellular water during growth, from birth to 16 years of age, presented on a double logarithmic scale.

The material has been analysed as for T and E. The averages of the logarithms of T, E, I, W, H and A have been calculated within the age groups and the results are presented in table 18.

The relationship between I and W and H is found to be:

$$I = C_I \cdot W^{0.998} \cdot H^{0.206}$$

where C_I is a constant that for the age groups II to V is: 0.166; 0.148; 0.157 and 0.166. The observed standard deviation of I from this relationship is 22.7 %.

TABLE 18

AVERAGE OF THE LOGARITHMS OF: T, E, I, W, H AND A OF THE SUBJECTS WHERE BOTH T AND E WAS MEASURED, AND THE ANTILOGARITHMS

	Age-group				
	I	II	III	IV	V
Number of observations	5	9	7	9	1
average of log T : $\bar{t}$ antilog $\bar{t}$	0.420 2.62	0.476 2.99	0.721 5.26	0.946 8.85	1.441 27.6
average of log E : $\bar{e}$ antilog $\bar{e}$	0.153 1.42	0.140 1.38	0.361 2.30	0.526 3.36	0.876 7.51
average of log I : $\bar{i}$ antilog $\bar{i}$	0.076 1.19	0.189 1.55	0.470 2.95	0.735 5.44	1.303 20.1
average of log W : $\bar{w}$ antilog $\bar{w}$	0.535 3.42	0.611 4.08	0.930 8.51	1.134 13.6	1.634 43.0
average of log H : $\bar{h}$ antilog $\bar{h}$	1.712 51.5	1.735 54.3	1.852 71.0	1.972 93.8	2.188 154.2
average of log A : $\bar{a}$ antilog $\bar{a}$ (days and years)	0.200 1.5d	1.697 50d	2.464 291d	3.011 2y 295d	3.687 13y 120d

When I is calculated as per cent of W within the age groups, the relative standard deviation is only 20.8 %. (In this connection attention is drawn to

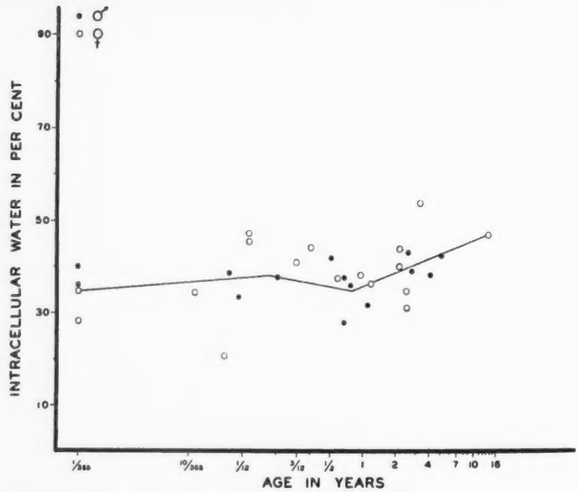

Fig. 11. Intracellular water in per cent of body weight related to age on a semilogarithmic scale. The curve is drawn through the average values of the age-groups I to V (table 19).

the fact that 22.7 % has been based on 20 degrees of freedom against 22 degrees of freedom in the latter case).

The intracellular water in per cent of body weight has been plotted against age on a semilogarithmic scale in figure 11 and the average values within the age groups and their standard errors are given in table 19. A small, but insignificant, increase is found from 34.8 per cent to 39.9 per cent from age group I to IV (1.2 times the standard error). In group V only one determination has been carried out and the result, 46.7 per cent, is somewhat higher than the 35 to 45 per cent usually stated as the normal value of I in adult subjects.

I have also been calculated in liters per square meter and the results are given in table 19. In this case, a gradual increase is found from 5.64 l/sq.m. in newborns to 14.64 l/sq.m around puberty, which is almost the same as the 14.2 l/sq.m. found in an adult male (Edelman, Olney, Kames, Brooks and Moore, 1952).

In order to compare I, E and T in per cent of W, the average values within each age group and their standard errors are presented in table 20. These values of T are not the same as those given in table 11, the reason being that table 11 has been calculated from all observations of total body water, whereas the mean values of T in table 20 are based only upon the measurements on those subjects where both T and E have been carried out. Furthermore, the values in table 20 have been calculated from the means of the logarithms of

TABLE 19

I IN PER CENT OF BODY WEIGHT, AND IN LITERS PER SQUARE METER SURFACE AREA, AND STANDARD ERROR (S. E.)

	Age-group				
	I	II	III	IV	V
I/W in % (S. E.)	34.8 (3.2)	37.9 (2.6)	34.7 (2.7)	39.9 (2.8)	46.7 (9.7)
I/SA in l/sq.m. (S. E.)	5.64 (0.52)	6.54 (0.45)	7.50 (0.59)	9.27 (0.64)	14.64 (3.03)

TABLE 20

T, E AND I IN PER CENT OF BODY WEIGHT AND THE STANDARD ERRORS (S. E.)
(IN PATIENTS WHERE BOTH T AND E WERE MEASURDE)

	Age-group				
	I	II	III	IV	V
T/W (S. E.)	76.7 (2.7)	73.3 (2.0)	61.8 (1.9)	64.9 (1.7)	64.1 (5.1)
E/W (S. E.)	41.6 (2.8)	33.7 (1.7)	27.0 (1.5)	24.6 (1.3)	17.5 (2.6)
I/W (S. E.)	34.8 (3.2)	37.9 (2.6)	34.7 (2.7)	39.9 (2.8)	46.7 (9.7)

T, E, I as the antilogarithms of these means. Therefore the sum of E and I in per cent is not quite equal to T in per cent.

When both T and E in per cent are decreasing during growth and I in per cent remains constant or even increases slightly, one may draw the conclusion that the decrease of T mainly is related to the decrease of E.

A further discussion of the physiological signifiance of these changes in body water compartment during growth will be given below.

Chapter 5.

CHANGES IN BODY WATER COMPARTMENTS DURING GROWTH

BLOOD AND PLASMA VOLUMES DURING GROWTH

During the last two decades, a dozen or more observations of the blood volume in children during growth have been carried out, most recently by: Morse, Cassels and Schultz (1947), Russell (1949) and Ely and Sutov (1952). The results obtained by these investigators are strikingly similar. Plasma volume as measured by the dye-methods, remains constant during growth at values of about 50 ml. per kg of body weight. Blood volume, calculated from the hematocrit and the plasma volume, is found to be about 80 ml. per kg with a slight tendency to increase around puberty, due to increase of the hematocrit values. Within all age groups, however, great variations are found, so it proved impossible to state normal values in spite of attempts to make correlations between blood volume and body weight, height, surface area, chest circumference and other body indices.

CHANGES IN TOTAL, EXTRACELLULAR AND INTRACELLULAR WATER VOLUMES DURING GROWTH

In the preceding chapters the material has been divided rather arbitrarily into different age groups for statistical treatment, and it has been shown that the simplest estimate of the fluid volumes is obtained, when calculated as per cent of body weight, within the age groups.

Another divisions into more practical age groups is given in table 21, where average values are given for: 0–1 day, 1–30 days, 1–3 months, 3–6 months, 6–12 months, 1–2 years, 2–3 years, 3–5 years, 5–10 years and 10–16 years of life. The standard errors of these values have also been included. Since this table includes observations in subjects where total or extracellular water was measured alone, the sum of E and I is not quite equal to T.

In figure 12 all the observations of total, extracellular and intracellular water, expressed as per cent of body weight, are presented and the curves are drawn through the average values given in table 21.

From figure 12 it is possible to get an impression of the simultaneous changes in the three main body water compartments during growth. Similar curves have been drawn to illustrate the changes in the fetus, based upon the data of tables 3, 12 and 17.

It is of interest to note that the curves during late fetal life are in close agree-

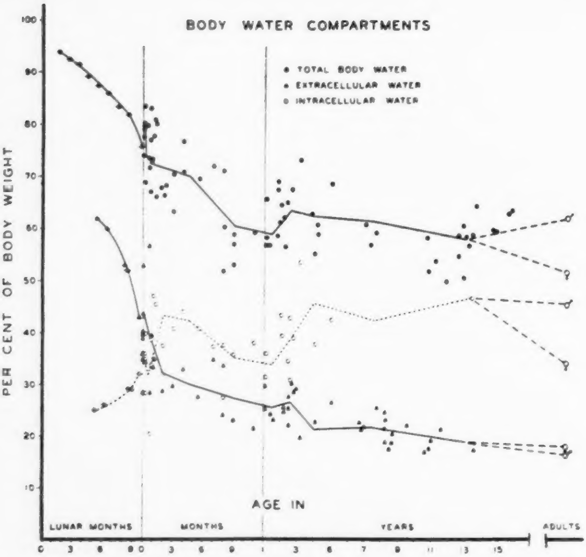

Fig. 12. Changes in total-, extracellular and intracellular water during fetal life and from birth to 16 years of age. The curves are drawn through the average values given in table 3, 12, 17 and 21 and are extended to corresponding normal values in the adult female and male subject.

ment with the corresponding curves during the neonatal period, in spite of the fact that the first set of curves is based upon histo-chemical studies, whereas the latter is based upon in vivo measurements.

In the fetus the following changes are observed: total body water decreases from 94 to 76 per cent from the first lunar month to the tenth. From the fifth to the tenth month extracellular water decreases from 62 to 43 per cent, whereas the intracellular water during the same period only increases from 25 to 32 per cent, the overall result being a decrease of total body water from 88 to 76 per cent during the last five months of intrauterine life.

This trend continues during postnatal life, from birth to somewhere between 1 and 2 years of age. Total body water decreases during this period from 79 to 59 per cent, corresponding to a decrease of extracellular water from 44 to 26 per cent, whereas intracellular water remains constant (between 35 and 43 per cent) and may even temporarily increase from 35 to 43 per cent during the first 3 months of life. During this period the curve for intracellular water intersects the extracellular curve. From that period onwards the intracellular phase constitutes a higher proportion of the body than the extracellular.

TABLE 21

T, E AND I IN PER CENT OF BODY WEIGHT DURING GROWTH AND THE NUMBER OF OBSERVATIONS AND STANDARD ERRORS (S. E.) IN EACH GROUP

Age	Per cent of body weight			Number of observations of:		
	T/W	E/W	I/W	T (S. E.)	E (S. E.)	I (S. E.)
0– 1 day	79.0	43.9	34.7	6 (2.6)	4 (3.3)	4 (3.6)
1–30 days	74.0	39.7	31.8	9 (2.0)	4 (3.0)	4 (3.3)
1– 3 months	72.3	32.2	43.3	7 (2.2)	3 (2.8)	3 (5.2)
3– 6 months	70.1	30.1	42.1	5 (2.5)	3 (2.6)	3 (5.1)
6–12 months	60.4	27.4	35.2	8 (1.7)	5 (1.9)	5 (3.3)
1– 2 years	58.7	25.6	33.8	5 (2.1)	4 (1.9)	2 (5.0)
2– 3 years	63.5	26.7	38.3	9 (1.7)	8 (1.4)	6 (3.2)
3– 5 years	62.2	21.4	45.7	5 (2.2)	2 (2.3)	2 (6.7)
5–10 years	61.5	22.0	42.3	4 (2.5)	13 (0.9)	1 (8.8)
10–16 years	58.0	18.7	46.7	15 (1.2)	5 (1.3)	1 (9.7)

Between 1 and 3 years of life a slight increase is found in all three body water compartments. From then on the extracellular water decreases gradually to 19 per cent at puberty, which is only slightly higher than the values found in adult men and women. In contrast to this both total and intracellular water display great variations around values similar to those found in adults.

No attempt has been made to make a statistical verification of this analysis of figure 12, since it is realised that the observations are too few and scattered and the individual variations too big to draw any definite conclusions. It is felt, however, that the curves give a general idea of the changes found during infancy and childhood.

The changes in body composition during the life span have been studied extensively in both human subjects and in animals. In such studies not all investigators have differentiated between "growth" and "ageing", although these two processes are not necessarily the same. On the other hand it is difficult or even impossible to define where one stops and the other gradually takes over. Since the present investigation only deals with observations in young, not yet fully developed subjects, the changes observed will be related to "growth".

Moulton (1923) studied the chemical changes in animals throughout the life span and came to the conclusion that a rapid decrease in the relative water content took place during early life until "chemical maturity" was reached, after which time only minor changes were observed. In different animals this

maturity was reached at an age which corresponded to 4.4 per cent of the total age. If the life span of the human is assumed to be 70 years, »chemical maturity« should be reached at about 3 years of age, which is much later than the 1 to 2 years found in this study.

So far we have only dealt with changes in the composition of the whole body during growth, but these may reflect: 1) similar changes in the composition of all tissues, 2) different alterations in different tissues, 3) changes in the proportion between different organs with different composition during growth and 4) changes in the amount of fat tissue in the body. Since all four factors may be at play during growth, it is necessary to carry out histo-chemical studies of separate tissues to get further information about the nature of these changes.

Lowry and Hastings (1942) have written a very fine discussion of these problems. They arrived at the conclusion that growth of tissues is associated with a relative increase in the proportion of the cells and a resultant decrease in the relative amount of extracellular fluid, whereas any marked alteration in the composition of the intracellular and extracellular phase not were observed.

By recalculating data from the litterature, they were able to demonstrate an increase in the proportion of cells in the human fetus, from 325 gram cells per kilogram "net" tissue (fat-free and bone-free) at 4 lunar months to 500–600 gram at term followed by a gradual increase to the adult level of approximately 700 gram cells per kilogram "net" tissue. Thus the proportion of cells increases at the expense of the extracellular phase, and since the extracellular phase only contains about 1 per cent solids, whereas the cells have a constant composition with approximately 310 g solids per 1000 g cells, the net results is a decrease of the total water content.

McCance and Widdowson (1954), who have contributed largely to a better understanding of the chemical aspects of growth and development, have recently published investigations showing that the nitrogen – potassium ratio increases during fetal life, indicating changes in cell composition. This finding is in contrast to the results of Lowry and Hastings, but the discrepancy may to some extent be accounted for the fact that McCance and Widdowson have included the minerals of the bones in their calculations. The question of whether the composition of the cells is changing or not during growth is therefore not setled yet.

The effect of growth on the distribution of water and electrolytes in muscle, liver and brain of cats has been studied by Yannet and Darrow (1938). They compared two groups of animals, one including animals of 1 to 2 months of age, and the other from 2 months up to maturity. This would in man be the equivalent of 1 to 3 years of age and from 3 years and older. Unfortunately they did not include the very young animals in which the most pronounced changes might be expected.

In the muscles, growth was associated with an increasing size of the individual muscle cells and a relative decrease of the interstitial phase. At the same time extracellular water decreased from 22 to 12 per cent, and intracellular water expanded from 57 to 65 per cent with a corresponding decrease of total body water from 79 to 77 per cent.

Growth of the liver was histologically a mere reduplication of the liver lobules; chemically a small rise in the fat content was found. At the same time the extracellular water decreased slightly from 24 to 21 per cent, intracellular water remained nearly constant and the total water content decreased accordingly from 73 to 71 per cent.

In the brain the changes were less clear. An increasing size of the nerve cells and dendrites was found and extracellular water decreased from 34 to 30 per cent. A small rise in intracellular water, from 50 to 51 per cent, took place and the total water content decreased from 85 to 81 per cent.

Kerpel-Fronius (1937) drew attention to the fact that not only does the relationship between extra- and intracellular water in different organs change during growth, but so does the relative proportion of water found in the same organs. Thus the muscles of the newborn baby contain 29 per cent of total body water, of which more than one third is extracellular (11 per cent), and while the total muscle-water in the adult increases to 51 per cent of total body water, due to the increasing proportion of muscles in the body, the relative amount of extracellular water of muscles remains unchanged at 11 per cent of total body water.

Similar calculations may be made for the water of the skin and subcutanous tissue. The total water constitutes 21 per cent in newborns, with 15 per cent extracellularly, in contrast to 9 per cent total skin-water in adults, with 8 per cent extracellularly. This shows that adult skin relatively has more extracellular water than that of the baby, but on the other hand the proportion of skin water has decreased. Total water of the central nervous system in new-born is 11 per cent, with 6 per cent extracellularly, and in adults 2 per cent, with 1 per cent extracellularly.

The three organs taken together contain in the newborn 61 per cent of total body water of which 32 per cent is outside the cells and 29 per cent inside. In the adult the total water remains at 62 per cent, of which only 20 per cent is extracellular, whereas intracellular water rises to 42 per cent.

Fat tissue contains very little water, only about 10–20 per cent. Any increase in the fat tissues of the body will therefore cause a decrease of the relative water content. Great individual variations are found in the relative fat content of the body, but certain average values may be given: at 5 lunar months the fetus only has ½ per cent fat tissue (Iob and Swanson, 1934), increasing to 12–16 per cent at birth (Widdowson and Spray, 1951). In the young adult subject

13 per cent fat is found in the female and 9 per cent in the male, increasing to 25 and 19 per cent at 55 years of age (Behnke, 1953).

To conclude this discussion, it appears that the relative decrease of total body water found during growth corresponds to a decrease of the relative volume of extracellular water, which again may be related to 1) increase in the relative amount of cells found in most tissues and 2) a disproportionately higher development of such organs as muscles, that have a high fraction of intracellular water, and 3) changes in the amount of fat tissue.

Chapter 6.

SUMMARY IN ENGLISH

CHAPTER I. Medical writings through the centuries reflect the great interest always shown in the humors or fluids of the body. Even the early Greek and Arabian physicians considered that the water content of the fetus was relatively greater than that of the adult.

Actual measurements of the total body water were not made until a hundred years ago. Determinations, made then and during the following decades, were by desiccation. Nearly all the observations were made on fetuses, but some were also made on children and adults.

These classical studies, as well as more recent ones, have confirmed that a gradual drying out process with a relative decrease in total body water takes place during fetal life and post-natal growth. Recent investigations have also shown that there is a relative decrease of the extracellular fluid volume during early childhood. Little, however, is known about the changes in the volume of intracellular water.

The present study was undertaken to clarify some aspects of the changes in body water compartments during growth, by measuring both extracellular and total body water in a number of infants and children. The volume of intracellular water has then been estimated by subtracting the extracellular from the total body water.

Different methods for the measurement of total body water and extracellular water are briefly discussed, as well as the reasons for selecting the heavy water method and the thiosulfate method respectively for these determinations.

The material consists of 93 subjects. Total body water alone was measured in 42, extracellular water alone in 20 and both total and extracellular water simultaneously in 31. The subjects ranged from newborn babies to children sixteen years of age.

CHAPTER 2. Previous studies of total body water in the fetus and in children have been collected from the literature and the results are presented in tables. A decrease from 94 to 76 per cent has been found in the fetus during intrauterine development.

The values of total body water obtained in the present investigation have been submitted to statistical analysis in order to study the relationship between

total body water and the age, weight, height and surface area of the subjects. The material has been divided into five age groups: 0–11 days, 11 days – ½ year, ½ – 2 years, 2 – 7 years and 7 – 16 years. Formulae are given for these relationships. No sex difference is found.

The best correlation is found between total body water and a combination of weight and height (relative standard deviation = 7.9 %), a slightly better fit than that obtained by any of the other relationships: weight alone (relative standard deviation = 8.0 %), per cent of the weight (relative standard deviation = 8.1 %), surface area (relative standard deviation = 8.2 %) and height alone (relative standard deviation = 12.0 %) and age alone (relative standard deviation = 18 %).

It is therefore concluded that for clinical purposes, the simplest estimate of total body water is obtained by calculation in per cent of body weight, within the different age groups. When calculated this way total body water is found to be: 77.6, 72.2, 59.5, 63.1 and 58.4 per cent of body weight in the age groups I to V. Thus there is a rapid decrease during the first one to two years of life.

When total body water is expressed as liters per square meter of surface area a gradual increase is found: 12.6, 12.3, 13.2, 14.7 to 17.9 liters per square meter in the five age groups.

In order to illustrate the changes of total body water during the total life span, corresponding values of total water and body weight have been plotted against each other on a double-logarithmic scale, representing subjects ranging from the first months of gestation to old age. This graph shows that a gradual "drying out" takes place which is most pronounced during the first year of post natal life.

Since no close correlation has been found between any of the above mentioned body measurements and total body water, it is impossible to define any exact normal value for a given child. A fairly good estimate may be given when the age and weight are known, but for investigational purpose, body water has to be measured whenever accurate values are needed.

CHAPTER 3. The few data on extracellular water in the human fetus given in the literature are presented in a table. These data show a gradual decrease from 62 per cent at five months of gestation to 43 per cent at full term. Similar data in children, obtained by various methods, show that this decrease is continuing during the first year of life.

The present data for extracellular water have been analysed in the same way as total body water. No sex difference has been noted. Similar standard deviations are found whether extracellular water is related to a combination of weight aid height (15.2 %), to per cent of weight (15.2 %) or to surface area (15.3 %).

The simplest way to calculate the extracellular water volume is therefore again as per cent of body weight. The following values have been found in group I to V: 41.6, 33.7, 26.2, 24.7 and 19.9 per cent, which is a gradual decrease throughout childhood.

Extracellular water expressed as liters per square meter of surface area shows a remarkable constancy within the age groups: 6.7, 5.8, 5.9, 5.9, and 5.6 liters per square meter. This constancy may partly explain the close relationship found between kidney function and surface area in infants and children.

CHAPTER 4. The few calculations of intracellular water in the human fetus indicate an increase from 25 to 32 per cent during the last five months of gestation.

The volume of intracellular water has been calculated by subtraction in the 31 children where both total and extracellular water were measured simultaneouly. No difference is found between the sexes. The material has been analysed as for total body water and extracellular water. When intracellular water is related to a combination of weight and height a relative standard deviation of 22.7 % is found, whereas the deviation is 20.8 % when calculated as per cent of body weight.

Intracellular water calculated in per cent of body weight within the age groups is 34.8, 37.9, 34.7, 39.9 and 46.7 (: only one determination) per cent, which shows that intracellular water in per cent of body weight almost constant during childhood. When expressed in liters per square meter surface area, intracellular water increases gradually: from 5.6, 6.5, 7.5, 9.3 to 14.7 liters per square meter.

CHAPTER 5. The changes found in body water compartments, in per cent of body weight, during growth may thus be described as a rapid decrease of total body water during the first year of life, with a similar decrease of extracellular water, whereas intracellular water remains practically constant. A slight increase of all three compartments is then observed from one to two years of age. During the later part of childhood a continuous decrease of extracellular water is found, whereas only minor changes of total and intracellular water are seen. These changes are demonstrated more clearly when the material is divided into smaller age groups and a figure has been constructed that illustrates the changes of both total, extracellular and intracellular water during intrauterine and post natal life up to sixteen years of age.

The significance of these changes are discussed in relation to changes in body composition during growth, which mainly may be described as: 1) a relative increase in the proportion of cells in most tissues at the expense of extracellular fluid, 2) a disproportionately higher development of such organs as muscles, that have a high proportion of intracellular water, and 3) a varying amount of fat tissue in the body.

RESUME

KAPITEL 1. De ældste medicinske håndskrifter viser, at man altid har været meget interesseret i legemets sammensætning, specielt legemets vædsker, og selv de tidligste græske og arabiske læger synes tillige at have været klar over, at legemets vandindhold ændredes under væksten, således at dette hos fostre var relativt større end hos voksne.

Nøjagtige bestemmelser af legemets totale vandindhold har man dog først udført de sidste 100 år. Dette blev udført ved udtørringsforsøg, som oftest på fostre; men man foretog dog også enkelte bestemmelser på børn og voksne. Først de sidste årtier har man haft andre metoder og kunnet måle såvel det totale som den extracellulære volumen.

Totalvandet inddeles almindeligvis i intra- og extracellulært vand. Det intracellulære vand udgøres af vandet inden i legemets celler, det extracellulære vand findes udenfor cellerne og kan inddeles i flere både anatomiske og funktionelle underafdelinger. Betydningen af disse underafdelinger diskuteres.

Enkelte undersøgelser har vist, at der foregår en gradvis mindskning af legemets relative vandindhold gennem fostertilværelsen og vækstperioden, og nyere undersøgelser har vist, at også den extracellulære vædske aftager gennem vækstperioden. Hvorledes intracellulære vædsker forholder sig har ikke været nøjere undersøgt.

Det foreliggende arbejde blev udført for nærmere at undersøge forandringerne i legemets forskellige vædskeafsnit under væksten, idet totalvandet og den extracellulære vædskes volumen er blevet målt hos ialt 93 børn, fra nyfødte til 16 års alderen. Det intracellulære vands volumen er herefter beregnet ved subtraktion.

De forskellige metoder til at bestemme det totale og det extracellulære vand gennemgås kortfattet og det konkluderes, at til den foreliggende opgave har det været mest formålstjenligt at bestemme totalvandet ved hjælp af tungt-vand metoden og extracellulærvandet ved hjælp af thiosulfat metoden. Man har så kunnet beregne mængden af intracellulær vand ved at subtrahere det extracellulære fra det totale.

Materialet består af 93 "normale" børn. Totalvandet alene blev målt hos 42 børn, det extracellulære vand alene på 20 børn og både total- og extracellulær vandet på 31 børn.

KAPITEL 2. Tidligere undersøgelser af totalvandet i fostre og børn er samlet i tabeller. Hos fostret aftager totalvandet kraftigt under udviklingen, hos børn har man ikke fundet en nærmere aldersvariation.

Resultatet af forfatterens egne målinger er blevet undersøgt statistisk, for at fastslå forholdet mellem totalvandets volumen og børnenes alder, vægt, højde samt overfladeareal. Materialet er opdelt i 5 aldersgrupper: 0–11 dage, 11 dage–½ år, ½ år – 2 år, 2 – 7 år og 7 – 16 år. Formlerne for de forskellige korrelationer er blevet udregnet. Der er ingen kønsforskel, og den bedste korrelation findes mellem totalvandet og en kombination af højde og vægt, (den relative spredning er 7,9 %), hvilket er noget bedre end korrelationen med vægten alene (den relative spredning er 8,0), med % af vægten (den relative spredning er 8,1 %), med overfladearealet (den relative spredning er 8,2 %), med højden (den relative spredning er 12,0 %), og dårligst er korrelationen med alderen alene (den relative spredning er 18,0 %).

Det konkluderedes derfor, at man til klinisk brug får det simpleste indtryk af totalvandet ved at udregne det i % af legemsvægten indenfor de forskellige aldersgrupper, og man har fundet, at det relative vandindhold er: 77,6; 72,2; 59,5; 63,1 og 58,4 % af legemsvægten i de 5 aldersgrupper. Det er således fundet, at det relative vandindhold aftager kraftigst gennem de første 1–2 leveår, og derefter forbliver nogenlunde konstant.

Hvis man udtrykker totalvandet som liter pr. m^2 overfladeareal, finder man omvendt en gradvis øgning fra 12,6; 12,3; 13,2; 14,7 til 17,9 liter pr. m^2 i de 5 aldersgrupper. For at anskueliggøre forandringerne i legemets totale vandindhold fra tidligste fostertilværelse til alderdommen, har man sammenlignet totalvand og legemsvægt i et dobbelt-logaritmisk koordinatsystem. Denne kurve viser ligeledes at den kraftigste »udtørring« finder sted i det første leveår.

Da man ikke har kunnet finde nogen snæver korrelation mellem totalvandet og nogle of de ovennævnte legemsmål, er det således umuligt at sige nøjagtigt, hvor meget et givet barns vandindhold er. En god tilnærmelse kan beregnes ud fra vægt og højde eller fra vægt alene, men en direkte måling er nødvendig, hvis man vil have et nøjagtigt tal.

KAPITEL 3. Tidligere målinger af den extracellulære vædskes volumen er samlet i en tabel. Denne viser en gradvis aftagen fra 62 % midt i fosterlivet til 43 % ved fødslen og at denne mindskning fortsætter i det første leveår.

Målingerne af det extracellulære vand i det foreliggende materiale er blevet statistisk undersøgt på samme måde som for totalvandet. Man finder ingen kønsforskel og korrelationen mellem extracellulært vand og en kombination af højde og vægt, overfladeareal eller udtrykt i % af vægten giver omtrent samme spredning, (15,2, 15,3 og 15,2 %), hvilket er en større spredning, end man finder for totalvandets vedkommende.

Det er således atter simplest at beregne det pågældende vædskeafsnit i % af legemsvægten, og man finder følgende værdier i de 5 aldersgrupper: 41,6; 33,7; 26,2; 24,7 og 19,9 %. Dette viser en gradvis mindskning gennem hele vækstperioden.

Udtrykt i liter pr. m^2 overfladeareal er den extracellulære vædske bemærkelsesværdig konstant. I de 5 aldersgrupper har man fundet: 6,7; 5,8; 5,9; 5; 9 og 5,6 liter pr. m^2. Det diskuteres, om dette sammenhæng er een af årsagerne til den snævre korrelation, der findes imellem nyrefunktionen og overfladearealet.

KAPITEL 4. De enkelte bestemmelser af det intracellulære vand hos fosteret, der findes i litteraturen, er anført. Der er fundet en gradvis stigning fra 25 til 32 % gennem de sidste 5 måneder af fosterlivet. I det eneste arbejde, hvor man har beregnet det intracellulære vand hos normale børn, fandtes fra 21,1 til 45,9 %, uafhængigt af alderen. I det foreliggende arbejde er det intracellulære vands volumen beregnet ved at subtrahere det extracellulære fra totalvandet. Man har ikke fundet nogen kønsforskel, og resultaterne er blevet statistisk behandlet som for de øvrige vædskeafsnit. Korrelationen mellem intracellulært vand og en kombination af højde og vægt giver en spredning på 22,7 %, hvorimod spredningen er 20,8 %, hvis man regner i % af legemsvægten.

Gennemsnitstallene indenfor de 5 aldersgrupper er 34,8; 37,9; 34,7; 39,9 og 46,7 (: kun 1 bestemmelse) % af vægten, hvilket viser, at det relative intracellulære vandindhold forbliver nogenlunde konstant under væksten. Udregnet i liter pr. m^2 finder man en gradvis øgning af intracellulærvandet fra: 5,6; 6,5; 7,5; 9,3 til 14,7 liter pr. m^2.

KAPITEL 5. Som konklusion af de ovennævnte undersøgelser kan man sige, når de forskellige vædskeafsnit udtrykkes i % af legemsvægten, at totalvandet aftager hurtigt gennem det første leveår, og at det extracellulære vand aftager gennem hele væksten, dog ligeledes hurtigst i det første år, hvorimod det intracellulære vand forbliver nogenlunde uændret bortset fra en ringe stigning i de første levemåneder. En lille øgning af alle tre væskeafsnit finder dog tilsyneladende sted fra 1 – 2 års alderen. Disse ændringer fremgår tydeligere, når materialet deles i mindre aldersgrupper, og værdierne for total, extra- og intracellulært vand gives for børn i alderen 0 – 1 dag, 1 – 30 dage, 1 – 3 måneder, 3 – 6 måneder, 6 – 12 måneder, 1 – 2 år, 2 – 3 år, 3 – 5 år, 5 – 10 år og 10 – 16 år.

Betydningen af disse ændringer diskuteres i forbindelse med forandringer i legemets sammensætning under væksten, idet der foregår 1) en relativ øgning af celleindholdet i de fleste væv på bekostning af den extracellulære fase, 2) en forholdsvis stærkere udvikling af sådanne organer som muskler, der har et højt indhold af intracellulært vand og endelig 3) en variation af legemets fedtindhold, der varierer omvendt med vandindholdet.

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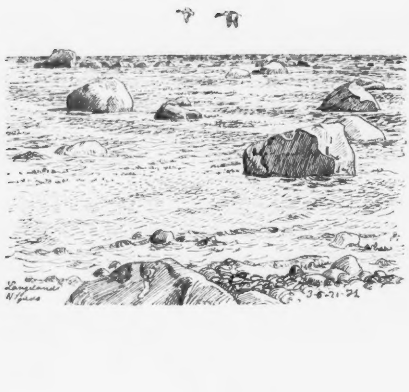

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CEREBRAL PALSY

A CLINICAL STUDY OF 370 CASES

For this work the authoress was awarded
H. M. the King's Gold Medal
at the University of Oslo,
September 3rd, 1956.

FROM THE CHILDRENS CLINIC, UNIVERSITY HOSPITAL
(RIKSHOSPITALET), OSLO, NORWAY
Head: PROFESSOR LEIF SALOMONSEN, M.D.

CEREBRAL PALSY

A CLINICAL STUDY OF 370 CASES

By

MARIT SKATVEDT

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Oslo, August 1956.

Marit Skatvedt.

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A. DEFINITION

Infantile cerebral paralysis—or cerebral palsy— is a clinical syndrome. It consists of a number of different forms of motor disorder due to cerebral lesions and is characterised by lack of control and coordination of the voluntary muscles.

The cerebral injury is acquired prenatally, natally, or in infancy, i. e. when the brain is still relatively undeveloped. This is probably why the injury is not fatal, but leaves these special forms of sequelae. The primary lesion is non-progressive. Thus the difference between this and other diseases with progressive motor defects, such as cerebral tumour, hereditary degenerative brain conditions, chronic encephalitis and so forth, is well-defined.

B. HISTORY OF THE STUDY OF CEREBRAL PALSY

During the last century a voluminous literature on cerebral palsy has appeared. Here only a few of the main features in the historical development of the study of the disease can be mentioned. The condition was first described by the English orthopaedist William John Little in his works: "On the Nature and Treatment of Deformities of the Human Frame" (1853), and: "On the Influence of Abnormal Parturition, Difficult Labours, Premature Births, and Asphyxia Neonatorum on the Mental and Physical Condition of the Child Especially in Relation to Deformity" (1862).

As is often the case in the history of medicine, the first description of the disease has become classical. Little recognised the etiological importance of birth trauma, of prematurity, and of neonatal asphyxia. His clinical observations were limited to the spastic diplegia, hence it came to be known as Little's Disease.

The next major publication to appear was "Die Infantile Zerebrale Kinderlähmung" (1897) by Sigmund Freud. He gave an excellent description of the various forms of cerebral palsy with precise classification of the different spastic symptoms. He also briefly mentioned the extra-pyramidal symptoms.

In Heubner's "Lehrbuch der Kinderheilkunde" (1906) the hyperkineses were discussed in the chapter entitled "Idiote". With a remark, however, that "cases occur with no suggestion of idiocy". His directions for the treatment of spastic paresis are sound: "Hot baths to relieve spasms, followed by careful passive and active movements, that should never be so violent as to excite the spasms,–and prostheses in suitable cases".

C. and O. Vogt (1920 and 1925) described changes in putamen and nucleus caudatus in bilateral athetosis.

The clinical picture of the disease was well described by George Peritz (1932) in "Die Nervenkrankheiten des Kindesalters": "Es handelt sich um Krankheiten, welche entweder angeboren, oder unter der Geburt erworben sind, oder Schlieszlich um solche, welche in den ersten Lebensjahren durch Infektionen hervorgerufen werden. Characteristisch für diese «Erkrankungen» sind als Symptome die Kontrakturen (spastische), welche entweder diplegisch, paraplegisch oder hemiplegisch auftreten können. Am Stelle diese Kontrakturen können auch andere Bewegungsstörungen wie die Cho-

rea oder die Athetose vorhanden sein. Als nicht konstante Symptome sind die Epilepsie und die verschiedenen Formen der Idiotie zu erwähnen".

Peritz saw no reason for making an etiological distinction between di- and hemiplegias, as the same factors may be responsible for both types. However, he found that consequent to infections of the central nervous system, hemiplegias are the more common. For many years the concept that "the diplegias were due to birth traumas and the hemiplegias to postnatal cerebral infections", prevailed in German medical circles.

Common to all these publications on the disease is a pessimistic view of the prophylaxis, prognosis, and therapy. This may explain the lack of medical interest in cerebral palsy up to recent times, despite the fact that the disease had been known for nearly a century, and had been clinically and neurologically well described. Cerebral palsy patients were invalids, hidden and generally considered mentally defective.

In 1940 the Americans W. M. Phelps and Earl R. Carlson showed that a high percentage of these patients–especially children with athetosis–dystonia–chorea, could be improved by treatment, and that most have normal intelligence. This declaration was a break with the pessimistic view, and in medical cirles it awakened new interest in the cerebral palsied patients.

In England, rehabilitation of cerebral palsied children was started by Eirene Collis and E. S. Evans at the Queen Mary Hospital, Carshalton.

Some recent major works on the subject should be mentioned: Alva Brochway's review of 1000 cases (1936),–Asher and Schonell's analysis of 400 cases (1950),–G. W. Anderson's complete survey of the etiological problems (1952),–and Meyer Perlstein's discussion of 334 cases of hemiplegia (1954). In his "Advances in Pediatrics" he described the modern view on the etiology, pathogenesis, classification of the clinical types, and "associated defects". The publication includes a comprehensive bibliography.

The frequency of the disease.

Cerebral palsy is a common disease. A few reports on the number of cases in some countries are available:

Phelps (1948) gives	about	4	children with the disease per 1000 births		USA
According to population statistics in Schenectady County (1949)	about	5.9	children	–"–	USA
Perlstein (1955) gives	"	5.0	"	–"–	USA
Scheel-Thomsen (1952)	"	1.5	"	–"–	Denmark
Nilsonne (1952)	"	0.6	"	–"–	Sweden
Asher and Schonell (1950)	"	1.0	"	–"–	England
Bjarne Andersen (1954)	"	1.9	"	–"–	Norway

C. SURVEY OF THE AUTHOR'S MATERIAL

Systematic treatment of cerebral palsy at Rikshospitalet was started in 1950. In the course of five years, 179 patients were admitted to the hospital and 191 were examined in the Out-Patient Department, making a total of 370 cases.

Those who were treatable and comparatively intelligent stayed in the hospital for some time, while the mentally defective were examined and sent home or referred to special institutions.

The cerebral palsied patients seen in the Out-Patient Department must be presumed to be more representative of cases occurring in the population in general. For in that department such patients were received for examination with no selection nor waiting time.

The majority of the patients were examined by the author. In the rare instances where this was not possible, the evaluation is based on case files.

The patients' age at the first examination appears in Table 1.

Table 1.

	Under 1 yr	1—2 yrs	2—3	3—4	4—5	5—7	7—10	10—15	Over 15 yrs	Total
Hemiparesis	14	24	12	1	5	16	7	9	1	89
Bilateral spasticity	10	13	23	19	15	19	12	9	1	121
Athetosis	3	9	4	3	1	8	15	5	5	53
Ataxia			4	1	3	6	9	1		24
Mixed group	19	11	8	10	5	9	7	13	1	83
Total	46	57	51	34	29	58	50	37	8	370

Electroencephalography (EEG) was carried out on 223 patients. Due to limited facilities at the EEG Department during the first years of the work with cerebral palsied patients at Rikshospitalet, examination of all was not possible. Most of the patients were examined once. A few with epilepsy had regular EEG examinations.

Pneumoencephalography (PEG) was not included for all patients during the first part of the period. In recent years, however, all had PEG examination, if not medically contraindicated or specially objected to by the parents. 105 patients had such examinations. In 26 it was unsuccessful or the interpretation difficult. In 79 cases PEG was successful, i. e. 21 % of the total case material.

The technique was as follows:

Most patients were examined under intratracheal general anesthesia. Those under one year of age as a rule had no general anesthesia, but were given rectal medication of Narcotal or some similar preparation. Withdrawal of fluid and air injections were alternated, about 5 c.cm. at a time. The total amount of air injected varied according to the age and size of the child, from 15 c.cm. in the youngest up to 40 c.cm. in the oldest, rarely more. The patients were examined both in a sitting and reclining position.

The intelligence was tested in 212 patients by various psychologists. The Terman-Merril Test was used when possible. When this was unsuited, the Leiter International Performance Tests were applied. Often both of these tests were used, and showed good correlation. Some of the most mentally defective were evaluated by the Bühler-Hetzer and Gesell developmental tests.

The following is a survey of the etiological and clinical conclusions regarding cerebral palsy based on the findings of this study. The findings were obtained partly from case history informations provided by the parents, concerning family conditions, pregnancy, birth, and later physical condition of the child, and partly on the results of the clinical examination.

D. ETIOLOGICAL CONSIDERATONS

In late years, the etiology of cerebral palsy has been the subject of intensive studies. Clarification of this side of the problem would enhance the possibility of finding an adequate prophylaxis.

The definition of the disease suggests that its origin lies in injury to the brain at an early stage of development, before, during, or relatively soon after birth. A division of the etiological factors into three main groups generally is accepted:

1) Prenatal factors.
2) Natal factors.
3) Postnatal factors.

For the postnatal factors, no definite time-limit has been established.

Wide disagreement prevails regarding the relative importance of these causal factors, and the actual nature of the injuries within the three time-segments. The problem is complicated by the fact that injuries of widely different nature–genetic, toxic, infectious, vascular, and asphyxial,–appear to be capable of producing similar neurological symptoms. The decisive factor seems to be the stage of development of the brain when injured.

The genetic anomalies result in developmental defects in various parts of the brain.

All traumas sustained by the mother which may influence the fetus theoretically are capable of causing brain injuries and result in cerebral palsy.

A thorough evaluation and a comprehensive list of references on the possible etiological factors are given by George W. Anderson (1952).

It seems reasonable to suspect that temporary deficiency of oxygen supply to the fetus is the most frequent factor responsible for brain damage. Intrauterine anoxia may result from uterine hemorrhages, placental infarctions, compression of the umbilical cord, premature separation of placenta, degenerative placental changes on prolonged pregnancy, or reduced oxygen tension in the maternal blood. Fetal cerebral lesions may be due to toxemia of pregnancy, the vaso-spastic substance of which may produce hypertension encephalopathy also in the fetus. Further, prenatal cerebral injuries may be caused by infections: lues, toxoplasmosis, and infection by neurotropic vira

in the first trimester of pregnancy (rubella et al.). Roentgen or radioactive rays may injure the fetal brain.

In animal experiments, Wilson and Barth (1949) showed malnutrition—particularly vitamin insufficiency—capable of causing deformities in the offspring. No similar observations have been made in man. However, the condition might explain why a diseased endometrium or unfavourable implantation of ovum often leads to abortion or deformities. Finally, maternal hormonal disturbances may produce deformities in the child. The frequent occurrence of deformities in the children of diabetic mothers is well-known. Neither should the old popular belief, that cerebral palsy may be caused by maternal psychic impressions, be entirely rejected. Freud declares mental injuries a not unimportant causal factor. Psyche, hypophysis, and adrenals are intimately related. Animal experiments have shown that cortisone injections into pregnant mice can produce deformities in a great number of the offspring.

The natal fators also may be of widely different kinds. Mechanical birth injuries may cause slight or extensive hemorrhages. Anoxemic injuries from cerebral ischemia during birth, or anoxia due to neonatal respiratory disorders may occur. Or the injury may be of a chemical nature, as most authors suggest is the case in kernicterus.

The postnatal factors include cerebral inflammations, vascular lesions, and anoxemic injuries to the child's brain in infancy. The concept of acute infantile hemiplegia has recently been suggested as a cause of spastic hemiplegia.

Before discussing the importance of the various etiological factors, data from the author's own patient material will be presented.

Distribution by Sex.

Table 2.

	Male	Female	Total	Male %
Hemiparesis R.	28	23	51	
Hemiparesis L.	26	12	38	
Bilateral spasticity	74	47	121	
Athetosis	32	21	53	
Ataxia	16	8	24	
Mixed group	49	34	83	
Total	225	145	370	60

The noticeable predominance of boys in all the groups of the material (60 %) is in agreement with the reports of other authors. Brochway (1936) in 1000 cases found 55 % of boys, Asher–Schonell (1950) in 400 cases reported 57 % males.

Birth Order.

Table 3.

Child No.	1	2	3	4	5	Over 5	Total	First child, %	No. inform.
Hemiparesis R.	25	10	5			1	51	68.6	
Hemiparesis L.	23	11	1	2		1	38	60.5	
Bilateral spasticity	59	29	16	6	5	3	118	48.8	3
Athetosis	22	15	9	4	1	1	52	41.5	1
Ataxia	13	7	2		2		24	54.2	
Mixed group	40	16	20	3	2	1	82	48.8	1
Total	192	88	53	15	10	7	365	52.7	5

In the total population of Norway in 1952, 38.4 % of the live births were first children. For the years 1936–1940 the percentage was 41 (The Central Bureau of Statistics.)

As regards five adopted children included in the material, information of their birth order was lacking. In the rest, the predominance of first-born children is statistically significant: 192 of 365 patients, i. e. 52.7 %.

Asher and Schonell's material shows about the same proportion of first born children, namely 56.4 % among 400 patients.

The percentage of first-born children is interesting, and seems to correlate with the well-known incidence of stillbirth and neonatal mortality by birth order. The mortality rate for the first-born is relatively high; it is the lowest for the second, and rises successively to the level of the first birth.

Salomonsen's Propedeutic Pediatry (1952) gives the following frequency for stillbirths per 1000 births (Gould 1938):

Birth No. 1	–	3.2 ‰	Birth No. 6	–	3.2 ‰
" " 2	–	1.0 "	" " 7	–	3.4 "
" " 3	–	2.2 "	" " 8	–	3.7 "
" " 4	–	2.5 "	" " 9	–	4.1 "
" " 5	–	2.8 "	10 and more	–	5.1 "

Professor Salomonsen comments: "The explanation may presumably be sought in the greater physiological adaptibility to pregnancy (by endometrium, uterine blood supply, and so forth) of the multipara than of the primigravida, and that with frequent pregnancies and older age, a reduced fitness of the mothers to give birth occurs".

Hereditary. Genetic Factors.

Consanguinity of the parents was reported in two cases. In one family there were two brothers with spastic paresis and two healthy children. In the second, a pair of binovular twins, one with spastic paresis, the other normal.

In addition, the material includes a brother and sister who both had spastic paresis. In these cases, no special etiologic factor was demonstrable. Further, there are two pairs of twins where both the children have cerebral palsy. According to their birth-weights, all four were premature, the one pair with birth-weights about 1000 grams, the other 1700 grams and 1800 grams respectively. PEG showed cerebral deformities in two patients. One had partial agnesia of corpus callosum, and another (one of the above twins with birth-weights about 1000 grams) a septum pellucidum cyst. The identical twin of the latter has no septum pellucidum cyst.

Otherwise, the material gives no information of familial occurrence of the disease or of definite cerebral malformations.

Other Prenatal Factors.

Table 4 is based on information obtained in the examination of 365 mothers (those of the five adopted children not being available).

The table shows hemorrhage during pregnancy in 10 mothers (2.7 %), toxemia in 14 (3.8 %), mostly mild cases. Only one had eclampsia. Placenta previa occurred in two cases, and four mothers had anemia. The numbers do not exceed the general average for such pregnancy disturbances. Strand (1949) found toxemia of pregnancy (the City of Oslo 1938–1944) in 6.1 % of primiparae and in 3.9 % of pluriparae, eclampsia in 0.39 %, and 0.25 % of primi- and pluriparae respectively.

As for virus infections during pregnancy, there are reports of two cases of rubella in first trimester, one of hepatitis in the 6th month, one of herpes zoster in the 4th and 5th months, and one case of varicellae one week before parturition. None of the children showed other organic deformities referable to these infections.

One mother had diabetes, and one had vitium cordis.

There are no reports of roentgen or radium irradiation, nor of malnutrition of the mothers. But no detailed inquiry into the diet was made. None had suffered shock nor had been severely frightened during the pregnancy.

Table 4.

Morbid Conditions in the Mothers during Pregnancy.

	Hemorrhages during pregnancy													
	1st trimester	Later	Toxemia	Placenta previa	Eclampsia	Anemia and blood transfusion	Anemia	Virus infection 1st trimester	Virus infection later	Lues	Pneumonia	Vitum cordis	Diabetes	Polyarthritis
Hemiparesis R.	1	2	1	1		1			1		1			
Hemiparesis L.	1		1											
Bilateral spasticity		3	4			1	1	2	1	1				
Athetosis	1	1	2				1		1				1	1
Ataxia												1		
Mixed group	1		5	1	1					1				
Total	4	6	13	2	1	2	2	2	3	2	1	1	1	1

Natal Factors.

Evaluation of the etiological importance of perinatal lesions to cerebral palsy is difficult. In the neonatal period the clinical symptoms of such injuries may be lacking or ambiguous, so that the trauma in the case cannot be definitely established. Convulsions in the new-born may be due to disturbances in the calcium metabolism as well as to a primary cerebral lesion. Asphyxia may be of cerebral or of cardiac or pulmonary origin. A numerical evaluation of the etiological importance of perinatal injuries in the present material therefore can only be based on the causes known to predispose to perinatal death from cerebral injuries: pathologic birth and prematurity. Clinical symptoms presumed to be either a direct consequence of, or responsible for cerebral injury, namely convulsions, asphyxia, and pathologic jaundice must be included.

Table 5.

The Birth.

	Normal birth	Breech-foot presentation	Face-brow presentation	Cesarean section	Forceps delivery not specified	High forceps	Prolonged labour (over 24 hrs) or prolonged expulsion (over 2 hrs)	Precipitate birth	Not specified difficult birth	Number of patients	Number of pathalogic births (%	No informations
Hemipareses	40	8	1	2	9	1	18	4		89	51.8	5
Bilateral spasticity	71	6	2	3	4	1	15	6	2	121	34.5	11
Athetosis	31	5	1		2		7	3	1	53	38.0	3
Ataxia	10	3			3	1	5	1	1	24	58.3	
Mixed group	40	8	2	2	3	1	13	7	4	83	47.5	2
Total	193	30	6	7	21	4	58	21	8	370	43.8	21

Information concerning the course of birth was lacking for 21 patients. For the remaining, the mothers have described the birth as normal in 193 cases and pathological in 155, i. e. in 43.8 %. The relatively most frequent pathologic forms are protracted birth (37.4 %), breech and foot presentation (19.3 %), forceps and precipitate deliveries (13.5 % each), and Cesarean section (4.4 %).

Table 6.

(see overleaf)

Neonatal Asphyxia and Convulsions.

The numbers in brackets indicate patients with several symptoms, initial apnea and later asphyxial attacks, and/or convulsions or asphyxia plus convulsions.

For 15 patients information regarding the neonatal period was lacking. Of the remaining 355, 167 (47 %) had symptoms suggestive of cerebral injury. Ninety-one patients had protracted initial apnea. Duration of this condition in the individual cases is not known, but in every case the mother declared that the child had been worked on for a long time before it started to cry.

64 patients had asphyxial attacks after initial respiration. The numbers in brackets indicate the patients who also had initial apnea. 23 had convulsive

seizures in the neonatal period. Here the number in brackets gives those who also had other of the previously mentioned symptoms. For 28, the diagnosis of cerebral hemorrhage was made at the hospitals where they were born. In eight cases it was reported that the umbilical cord had been coiled several times around the neck. All showed symptoms of asphyxia.

Schultze's swinging technique–strongly disapproved by modern obstetrical textbooks,–had been used in six cases.

	Number of patients with asphyxia/convulsions	%	Specification					
			Initial apnea	Asphyctic attacks	Convulsions	Umbilical cord around neck	Schultze's resuscitations	Cerebral hemorrhage diagnosed in hospital
Hemiparesis R	22	42.7	14	9 (7)	3 (2)			7
Hemiparesis L.	16		6	4	3			5
Bilaterial spasticity	46	38.0	27	21 (4)	5 (4)	3	1	3
Athetosis	26	49.0	13	13 (4)	3 (1)	4		5
Ataxia	15	62.5	6	7	1		1	3
Mixed group	42	50.6	25	10	8 (2)	1	4	5
Total	167	47.0	91	64	23	8	6	28

Kernicterus.

According to the case histories, 15 patients had had clinical symptoms that strongly indicated kernicterus (somnolence, opisthotonous position, twitchings, and severe jaundice). Blood grouping tests of the 15, either at birth or on admission for suspected cerebral palsy, showed Rh incompatibility between mother and child,–Rh minus in the mother and Rh positive in the child,–and antibodies in the maternal blood. Nine of the patients had athetosis, while six with additional severe rigidity were recorded in the mixed group.

No case of ABO incompatibility was found in this material.

Two patients had had exchange transfusion a few hours after birth, but developed symptoms of kernicterus the third day. One had severe athetosis plus diabetes mellitus, the other, who is severely mentally retarded, pronounced rigidity. Four patients had received repeated small blood trans-

fusions. Six were treated at the Pediatric Department of Rikshospitalet in the neonatal period. The remaining nine received no treatment for their erythroblastosis.

Eleven patients had had severe and protracted neonatal jaundice with demonstrable cerebral symptoms of the same nature as described for the former group. The 11 showed no blood group incompatibility between mother and child by the Rhesus or ABO systems. Three had athetosis, one ataxia, and seven athetosis plus rigidity.

Two patients had hemolytic anemia, but do not belong in the kernicterus group. Nor did they show the usual sequelae after kernicterus, but spastic hemiparesis. One of them had congenital erythroblastosis and was treated with exchange transfusion at the Pediatrics Department of Rikshospitalet. The patient had no clinical kernicterus. The second patient was diagnosed as hemolytic anemia from unknown cause at the Pediatrics Department of the University Children's Hospital of Kiel, where she was admitted the first day of life. There was no blood group incompatibility between mother and child. Blood transfusions were given and recovery was rapid.

Of the 26 children who are believed to have had kernicterus, two were prematures, five had birth-weights over 4000 grams. One had pathologic birth and one neonatal asphyxia. These conditions may of course have contributed to the development of cerebral palsy in these cases.

Table 7.
Birth-weight.

	Under 2500 gms	2500—2999 gms	3000—3999 gms	Over 4000 gms	Number of patients
Hemiparesis R.	9	8	17	8	42
Hemiparesis L.	6	6	10	4	26
Bilateral spasticity	49	15	25	11	100
Athetosis	10	9	21	4	44
Ataxia		4	9	9	22
Mixed group	12	12	35	11	70
Total	86	54	117	47	304
%	28.2	17.8	38.5	15.5	
Aker Hospital					
2060 births	4.1	13.7	67.8	14.4	
U.S.A.	6.1	17.4	66.8	9.7	

The birth-weight was known for 304 patients.

The material confirms the big *prematurity* rate among such patients, as already pointed out by Little, and which is reported in all cerebral palsy publications.

Sunde (1930) gives a prematurity rate of 7.3 % among 22.191 births from the Obstetrical Department of Rikshospitalet for the years 1908–1922. The percentage is calculated from liveborn children.

Daa-Blegen (1952) found prematurity to be 5.4 % of liveborn children in the City of Oslo for the years 1930–1939.

Salomonsen (1954) reported prematurity in 4.1 % (birth-weights under 2500 gms) of 2060 liveborn children from Aker Hospital for the years 1946–1949.

In USA Weyman (1954) found 6.1 % with birth-weight under 2500 gms.

Table 8.

Birth-weight—Sex Distribution.

	Under 2500 gms Male–female		2500—2999 gms Male–female		3000—3999 gms Male–female		Over 4000 gms Male–female		Total
Hemiparesis R.	5	4	4	4	11	6	3	5	42
Hemiparesis L.	3	3	4	2	5	5	3	1	26
Bilateral spasticity	28	21	7	8	19	6	7	4	100
Athetosis	5	5	4	5	15	6	3	1	44
Ataxia			3	1	6	3	5	4	22
Mixed group	8	4	3	9	23	12	7	4	70
Total	49	37	25	29	79	38	28	19	304

Table 8 gives the sex distribution within the individual weight groups. The male predominance within the normal weight groups (3000–4000 gms) is marked, but the author ventures no conclusion from this observation.

A division of the prematures into two groups (Table 9), the very low (under 1500 gms) and the relatively high birth-weights (1500–2500 gms), shows a slight overweight in the former group. The numbers are small, however.

The corresponding values in a material from Aker Hospital are 12 % under 1500 gms and 88 % between 1500 and 2500 gms.

The predominance of bilateral spasticity in the very small premature children is of some interest.

Table 9.

	Birth-weight under 1500 gms	Birth-weight 1500—2499 gms
Hemiparesis R.		8
Hemiparesis L.		6
Bilaterial spasticity	11	38
Athetosis		10
Ataxia		
Mixed group	2	11
Total	13	73

Prematurity itself implies a greater risk of vascular and anoxemic cerebral injuries which may result in cerebral palsy. Table 10 illustrates the possible importance of other etiological factors.

Table 10.

	Course of Birth						
	Normal birth	Forceps delivery	Breech and foot presentation	Cesarean section	Precipitate birth	Prolonged birth	
Hemiparesis R.	4	2	2				
Hemiparesis L.	5						
Bilateral spasticity	34	1	1	2	3	2	
Athetosis	8	1	1				
Ataxia							
Mixed group	7		4			1	
Total	58	4	8	2	3	3	Pathologic birth 25 %

For eight patients there was no information of the course of birth. Cesarean section was performed in one case because of weakening of the fetal heart sound, and in one because of toxemia of pregnancy.

From the table it appears that pathologic birth is more rare among the prematures than in the total group.

The comparatively frequent occurrence of *heavy children* (birth-weights over 4000 gms) that appears in this material (15.5 %), is a condition rarely mentioned. If the number of premature cases is subtracted from the total cases from both Aker Hospital and this study, the percentage of children having a birth-weight of 4000 gms or more is 15 per cent of the Aker Hospital group as compared with 21.5 per cent found in this study. This is a significant difference.

Table 11.

Other Possible Etiological Factors in Children with Birth Weight over 4000 gms.

	Birth order			Course of birth					Peri- and postnatal factors			
	1	2	3 and more	Normal	Breech-foot-brow presentation	Prolonged birth	Precipitate birth	Forceps delivery	Asphyxia	Kernicterus Rh.	Cerebral embolism	Encephalitis
Hemiparesis R.	5	3		6	1		1		3		1	1
Hemiparesis L.	3	1		1	1	1		1	3			
Bilateral spasticity	3	4	4	6	1	4			4			
Athetosis	2		2	4					2	2		
Ataxia	2	4	4	3	2	4		1	6			1
Mixed group	3	5	3	7		2	1	1	7	3		
Total	18	17	13	27	5	11	2	3	25	5	1	2

The material includes 25 twin patients.

The information that twins were identical or fraternal was obtained in only eight cases.

The percentage of twins in the total material is 6.7, which is considerably more than in the total population. In Norway 1950 1.4 % of all births were twin births.

Table 12.

	Second twin normal	Second twin stillborn	Both twins cerebral palsy	Twin number (The other twin healthy) 1	2	Identical twins	Fraternal twins	Total number twin patients with cerebral palsy	
Hemiparesis R.	1	1			1			2	
Hemiparesis L.	2			2		1		2	
Bilateral spasticity	7	2	2	3	4	2	3	11	
Athetosis	1			1				1	
Ataxia	1				1		1	1	
Mixed group	3	3	2	2	1		1	8	
Total	15	6	4	8	7	3	5	25	

Postnatal Factors.

Table 13.

	Meningitis	Encephalitis	Whooping cough	Asphyxia during a cold when 3 weeks old	Thrombo-embolism	Epileptic seizures	Total
Hemiparesis R.	2	3			1	2	8
Hemiparesis L.		3				1	4
Bilateral spasticity	1						1
Athetosis			1				1
Ataxia		2		1			3
Mixed group		1					1
Total	3	9	1	1	1	3	18

The 12 patients who had meningitis or encephalitis had all been normal before the onset of the disease. The youngest one, who had staphylococcus meningitis during an umbilical sepsis, was admitted to the Pediatric Department of Rikshospitalet. Hemiparesis ensued. Another child had hydrocephalus in connection with meningitis when five weeks old. One was 10 months old when he had meningitis followed by hemiparesis. The age of the encephalitis patients was 8 months, 9 months, 1 year for two, 14 months, 15 months, 1½ years for two, and 2 years. All of the patients had developed normally, physically and mentally, before the encephalitis.

The patient in whom whooping cough is believed to be the etiological factor, had normal birth and neonatal period. When three weeks old he had whooping cough, accompanied by several attacks of asphyxia. The patient for whom asphyxia during an ordinary cold is presumed the etiological cause, had normal birth and neonatal period. When three weeks old he caught a cold and had several asphyxial attacks.

The thrombo-embolism patient developed hemiparesis during a diphtheritic croup when four years old. The diagnosis of cerebral embolism was made at the Neurologic Department of Oslo City Hospital.

Discussion.

Some authors, among them the American neurologist F. R. Ford, stress the importance of *hereditary cerebral malformation* in the etiology of cerebral palsy. The frequent occurrence of pathologic birth, prematurity, and neonatal asphyxia they admit, but consider that they are the results of a primary deformity, not the cause of the disease.

Cases of familial spastic paraplegia, atonic diplegia, athetosis, and ataxia due to developmental defects of various parts of the brain have been described by Ford, Paskind, Wilson and Wolfson, Mathews and McDude, and others.

Cerebral palsy has been observed in identical twins with normal birth, in brothers and sisters where pregnancy and birth have been normal, and in several individuals distantly related. These are single observations, however, and the fact remains that in the great majority of the cerebral palsied, there appears to be no tendency to familial occurrence.

From the analysis of extensive cerebral palsy series, most authors have come to consider hereditary familial factors of minor importance (Freud, Lucas, Asher and Schonell, and others). The present material points in the same direction. In only two families may hereditary deformity be suspected. Otherwise, the material gives little clue to familial occurrence of the disease.

In two cases roentgen showed cerebral deformities that, however, cannot be considered to be the cause of the disease.

As mentioned above, it is theoretically quite possible that *prenatal fetal injuries* may result in cerebral palsy. The present material seems to give scant support to this theory. The pregnancy abnormalities recorded were hardly more numerous than in a normal population. If defective implantation, malnutrition of ovum, hormonal disturbances of other abnormalities had been the cause, more frequent reports of threatened abortion and hemorrhages during pregnancy would have been expected.

If exogenous injuries to the fetus were the cause, frequent occurrence of infective, actinic, or other maternal complications in the first trimester might be expected. The material gives no such information.

Prenatal fetal injuries very often produce multiple deformities. The most potent argument against an etiologic importance of such injuries to cerebral palsy in the present material, is that cerebral affection in the majority of patients was unaccompanied by signs of other isolated or multiple deformities. Malformation of the fingers was found in two patients. Two had cataract. No maternal illness or injury during pregnancy was reported in these cases. In Asher and Schonell's material (400 cases) congenital deformities were demonstrated in 2.6 %, against over 2 % of the English population in general.

However, our knowledge concerning prenatal injuries in man is as yet limited. It is based on scattered clinical observation and on animal experiments (Warkany, Wilson, Windle and others). Research in the field is just beginning, and conclusions regarding the etiological importance of this factor to cerebral palsy are apt to be hasty.

The histories of the cerebral palsied children of the present material frequently indicated one or more of the following four conditions: *Pathologic birth* (especially breech presentation and protracted birth), *asphyxia* or clinical evidence of *cerebral injury* at birth, *prematurity*, and severe *icterus*.

Of the four conditions, only *kernicterus* is generally and unreservedly recognised as a cause of cerebral palsy. The clinical picture of kernicterus is typical. It appears during the 2nd to 4th day of life, and usually is easily diagnosed. The mortality rate is about 50 %. Autopsy reveals degenerative changes and bilirubin imbibition of the basal ganglia, the grey matter of medulla oblongata and medulla spinalis, and of the cortex. It is generally agreed that children surviving the illness often develop cerebral palsy.

Kernicterus is in most cases due to erythroblastosis because of Rh or ABO incompatibility between mother and child. Even though the basic pathogenetic conditions of the disease are not clarified, it is a clinical fact that

its occurrence is directly correlated with the bilirubinemia level. Pathogenetically the low blood-liquor barrier during the first days of life may play a part.

It has been claimed that it is the indirect bilirubin that invades the central nervous system and has a toxic effect on the brain cells. Stempfel and Zetterström (1954) have shown that the bilirubin demonstrable in the new-born is indirect bilirubin. In jaundice conditions in adults, direct bilirubin is found in the spinal fluid (Amatuzio, Weber, and Nesbitt 1953).

Lately severe jaundice without blood-group incompatibility has been found to be capable of producing kernicterus in a new-born child (Goven and Scott 1953, Claireaux 1953, Black-Schaffer et coll. 1954, and others). This applies especially to prematures, in whom the blood-liquor barrier is more permeable than in those born at full term.

At Rikshospitalet in the last few years seven cases of very severe icterus have occurred in prematures without blood-group incompatibility between mother and child. Two children died from kernicterus, five had exchange transfusion and survived.

The present material includes 15 probable cases of kernicterus due to erythroblastosis, and 11 of probable kernicterus without blood-group incompatibility, i. e. 26 cases (7 %).

The clinical picture of the fully developed kernicterus is—as mentioned —easily diagnosed. It seems reasonable, however, that mild cases, although unrecognised in the neonatal period, may still result in cerebral palsy. The conclusion seems justified that severe icterus in the new-born, regardless of the blood-group conditions and clinical symptoms of kernicterus, is a relatively frequent cause of cerebral palsy. Formerly it was estimated at 8—10 % of all the cases. In late years the frequency definitely has been reduced, owing to the treatment of erythroblastosis by exchange transfusions.

Material from the Pediatric Department of Rikshospitalet (Amlie, Hagelsten, and Salomonsen, 1954) includes only two cases of cerebral palsy among 101 erythroblastosis patients treated with exchange transfusion, as against eight of 55 who did not have the treatment. Formerly exchange transfusion was used essentially for erythroblastosis foetalis. Comparatively harmless as is the method when performed by a trained staff, the treatment should be extended to cover all forms of severe icterus in the new-born. Bilirubin tests in the course of the first 3—4 days of life should be the routine for all prematures and for all jaundiced fullborn children. When exceeding 18—20 mg %, exchange transfusion should be considered.

The other three perinatal conditions common in the histories of cerebral palsied children, namely *prematurity*, *pathologic birth*, and *asphyxia/birth-*

traumatic injury, were mentioned already by Little as the main cause of the disease, and were thus regarded until 1920–30.

Since that time the etiological importance of these conditions has been questioned by a number of authors. In the last decade, however, the pendulum has swung back. Today perinatal injuries generally are considered to be the main factors.

Most authors agree that on retrospect examination of cerebral palsied children, these perinatal conditions appear relatively often. The strongest argument against their importance is a reversal of the procedure, namely follow-up examination of children with these perinatal conditions, who show no increase in the occurrence of cerebral palsy.

On follow-up examination of 213 children aged 1–4 years, with reports of pathologic protracted birth, Keith and Norval (1950) found signs of neurologic lesions no more frequent than in the control-group of children with normal birth. 4.8 % of those with protracted birth had neonatal asphyxia with absence of respiration up to 15. min. In these cases neurological lesions were no more frequent than in the non-asphyxial ones.

Campbell et al. (1950) made follow-up examinations of 61 children with histories of neonatal asphyxia, and found I.Q. not affected. McPhail and Hall (1941) arrived at the same result in the examination of 34 asphyxial children.

In the follow-up examinations of 1423 prematures from the Obstetrical Department of Rikshospitalet, Sunde (1930) found 7 % "defective children", 5.7 % of whom were mentally impaired. Only four had Little's disease, two had epilepsy, two reduced vision, and two speech disorders. But the mortality the first year was 35.8 %, and up to the age of seven it was 38.2 %.

Blegen (1952) found "Little's disease" in only 0.4 % of premature children born in Oslo between 1930 and 1939.

Not all examinations have given such negative results.

Darke (1944) gives statistically significant lowering of I.Q. in children with early severe asphyxia. Hellström and Johnson (1953) report cerebral lesion in no less than 18 of 65 asphyxial children. In the same material d'Avignon and Keilson (1953) found considerable pathologic EEG changes in the 18, and also slight EEG changes in a large number of children without clinical sequelae.

As pointed out by Benda (1952), Salomonsen and Skatvedt (1954), and others, negative follow-up examinations do not permit far-reaching conclusions concerning etiology, as the clinical symptoms observed in the newborn are not necessarily ascribable to the cerebral lesion that causes cerebral palsy. The pathology of the brain in children in relation to the birth trauma is

not yet sufficiently known to permit exclusion of the possible presence of anoxemic injuries that may cause cerebral palsy without giving clinical symptoms in the new-born. The brain of the new-born child is still in an undeveloped stage. In many cases, parts which are inactive at birth may be more injured than the relatively resistant vital centre in medulla oblongata. Therefore, no full correlation can be expected between a pathologic birth, clinically manifest cerebral lesion, neonatal asphyxia, and premature birth on the one side, and a later cerebral palsy on the other. Some connection seems probable, however. Even if proving causal relationships statistically is difficult, clinical observations point in that direction.

W. S. Craig (1950) mentions 593 new-born children with symptoms of cerebral hemorrhage, who grew up. Professor Craig is a pediatrician with wide experience in the pathology for the new-born. Even though the differential diagnosis between a cerebral hemorrhage from birth trauma and other pathologic conditions in the neonatal period is very difficult, it must be presumed that he has presented a pure cerebral hemorrhage collection of material. On follow-up examination of these children, aged 1/2 year to 5 years, he found cerebral palsy in 37 (hemiplegia in 17, monoplegia in 8, asymmetric bilateral paresis in 5, spastic diplegia in 2, athetosis or ataxia in 5 cases).

Strongly positive observations are reported with regard to the etiological importance of anoxemia. In animal experiments, W. F. Windle (1944) showed that sublethal anoxia induced by ligation of the uterine arteries, causes lasting cerebral injury in the young.

In the 1920's there were published several valuable pathologic-anatomical studies of the brains of children who died neonatally. These are of great interest in the study of the pathogenesis of cerebral palsy. The most important work is by Philip Schwartz. He described small punctate hemorrhages in the supply area of the Vena Galeni magna in as many as 65 % of the new-born. He believed the hemorrhages to be the result of an increased tension when the venous circulation is temporarily obstructed during birth, causing a negative pressure on the head. He assumed that the suction effect was transmitted to the central veins of the brain and caused congestion, thrombosis, and minor hemorrhages. The frequent occurrence of such small hemorrhages and cellular necroses in the brain of the new-born, and especially in the Vena Galeni magna area, has later been confirmed by others, but their pathogenesis has been debated. On the whole, Schwartz's theory has been abandoned, and the phenomenon is believed due to anoxemic injuries (Potter and others).

Very few autopsy reports of cerebral palsy cases are found in the literature. The reason probably is that these patients are admitted to hospital only

for examination and short periods of treatment, and that most of their lives are spent at home or in institutions.

One of the few reports of examinations is published by P. E. Benda (1945). In the majority of his cases he found pathologic changes generally localised to the Vena Galeni area, and of an appearance that, in his opinion, supports the theory of the small hemorrhages and necroses, originally described by Schwartz in the new-born. Benda's work has been subject to criticism, however.

The pneumoencephalographic findings in the present material will be discussed later. Here it will only be mentioned that in patients in this study, PEG indicated a location of the pathologic changes in cerebral palsy to the deep parts of the brain, in agreement with Benda's autopsy findings. The frequent symmetrical bilateral distribution of the motor disturbances in cerebral palsy would be most naturally explained by a location of the injury mainly in the supply area of a centrally situated vascular system, e. g. the Vena Galeni.

Today most authors believe perinatal injuries to be the main cause of cerebral palsy. The lesions must be presumed to be partly in the form of purely traumatic hemorrhages, partly as petechial bleedings from anoxemic endothelial injuries, and partly as cellular necroses from oxygen deficiency. The present material shows several conditions which support this theory.

The frequent occurrence of *asphyxia and/or symptoms of cerebral injury* in the neonatal period is in agreement with such a concept. The symptoms, however, cannot be considered definite evidence, as they may also arise from prenatal cerebral injury. Admitting that with a prenatally injured fetus the chances of a *pathologic course of birth* are increased, this hardly explains the predominance of pathologic births found in this and other materials. In this study breech presentation and protracted birth are especially frequent, both forms that may predipose to scattered anoxemic cerebral injuries. Protracted birth is well known as a frequent cause of neonatal asphyxia. Reid (cit. Clement Smith) gives the mortality for fullborn children with birth lasting over 20 hours at 11.6 %, over 40 hours at 29 %.

Prematurity is frequent in this study and in other materials. Premature children are predisposed to hemorrhages because of blood vessel fragility. Prematures who die in the neonatal period often show hemorrhages from the vena terminalis into the ventricular system (Gröntoft and others). This indicates that Vena Galeni and its branches are particularly vulnerable in the premature. In addition, they are noticeably predisposed to asphyxia.

It is evident that various prenatal factors often may play a part. Table 10

gives the factors, in addition to prematurity, that may have had etiologic importance.

The only possible explanation of the small, if statistically significant, predominance of ***big babies*** in this material seems to be that the cerebral palsy is a consequence of difficult birth in these cases. Overweight of the children can hardly be presumed due to prenatal injuries. If so, there would have to be maternal hormonal disturbances. No clue to such conditions is found, however.

The fact that these big babies are not postmatures should be stressed. Postmature children are injured intrauterinally because of degenerative changes in placenta. They are thin and their birth-weight is usually not above normal.

Table 11 shows about the same frequency of pathologic births among the overweight children as in the total cases.The predominance of neonatal asphyxia is a natural consequence of the more difficult birth in these cases. The relatively great number of kernicterus cases may be explained by the tendency to edema in children with erythroblastosis.

A number of attempts have been made to trace the various types of cerebral palsy back to special etiological factors. Kernicterus usually results in athetosis and rigidity, often accompanied by visual and auditory disturbances. Most investigators find the report of prematurity relatively frequent in patients with spastic diplegia. Perlstein (1955) states: "From the point of view of pathogenesis, anoxia is more likely to produce athetosis, while hemorrhage is more likely to cause spasticity". The view is often encountered in the literature without, it seems, being well founded.

Like other materials, this one shows predominance of prematurity in the group of bilateral spasticity. Further, kernicterus is seen to give athetosis-rigidity plus auditory defects. Otherwise, the material permits no conclusion regarding special etiological factors as the cause of special types. Anoxia, by most authors believed to be connected with athetosis, in the present material is rather evenly distributed in all groups. The percentage of pathologic birth is somewhat lower in the bilateral spasticity group. However, deduction of the prematures with normal birth, leaves about the same percentage of pathologic birth also in this group.

Conclusion.

Based on findings of the presents study and other materials, the author believes it probable that perinatal vascular and anoxemic brain injuries are the most frequent causes of cerebral palsy. As these lesions also are the main

causes of neonatal death, it seems an obvious conclusion that cerebral palsy is the result of the same injuries of a sublethal degree. This is clearly illustrated by G. W. Corner. He compares the etiological factors in 96 cerebral palsy patients born at Johns Hopkins Hospital, with those of perinatal death at the same place. He presents the results in the following table.

	Perinatal death 1954	Cerebral palsy
Anoxia	47.3 %	55.2 %
Prematurity only	9.6 %	5.2 %
Obstetric trauma	9.7 %	11.5 %
Infection	9.2 %	9.4 %
Malformation	9.6 %	–
Unknown	24.6 %	18.7 %

He believed prematurity alone to be the cause of cerebral palsy only in 5.2 %. But about one-third of his cerebral palsy patients were prematures. He concludes: "The mechanisms which produce dead infants and the mechanisms which produce damaged infants are the same. Whether an infant is damaged or dies is only a matter of the extent to which these mechanisms operate. Furthermore, it is apparent that anoxia is the most destructive force".

The reasons for the gratifying reduction in neonatal mortality in the last years are several. Better hygiene during pregnancy, wider knowledge of the pathology of the new-born, a delivery which is more lenient to the child, an adequate oxygen supply, clearing of the air-passage, the use of antibiotics are among the main ones. Continued development of these measures will also be important to the prophylaxis of cerebral palsy. Special attention should be called to a condition that seems rarely mentioned. In the present material, protracted birth represents the most frequent birth complication. In the author's opinion, this is where the obstetricians can make a real contribution. To omit artificial intervention to end a prolonged delivery, hoping for a "natural birth", means a considerable danger to the child.

In the further development of the prophylaxis certain dangers should be realised. Parallel to lowering of the neonatal mortality there is the risk of a corresponding rise in the number of children with sublethal lesions, who may later develop cerebral palsy, epilepsy, and become mentally impaired.

The role of the *postnatal injuries* as a certain, if less frequent cause of cerebral palsy, is generally recognised.

In the present material (see Table 13) late injuries, such as meningitis, encephalitis, whooping cough, cerebral embolism, and asphyxial seizures during an infection of the upper respiratory tract, occurred in 15 patients. Three other patients developed lasting hemiparesis after epileptic seizures. In these cases, however, the epilepsy itself suggests that cerebral lesions were already present. In one of the cases, the birth had been pathological. This leaves 18 patients, i. e. 5 % of the total material, in whom postnatal injuries may be presumed the cause of the disease. The number is somewhat lower than reported by other authors. Freud gives 7.7 %, Scheel Thomsen about 10 %, and Asher and Schonell's material shows 7 % after deduction of kernicterus, which they registered with "Acquired cerebral palsy", and for cases of progressive spastic paralysis. Perlstein reports 8–13 %.

The prophylactic measures, where postnatal cerebral palsy is concerned, are obvious. The reader's attention is drawn to the two patients in whom whooping cough and asphyxia during an upper respiratory tract infection are the suspected causes of the disease.

In 32 patients (8.3 %) no possible etiological factor–prenatal, natal, nor postnatal,–has been found. Clinically there is no difference between these patients and the rest of the material. Eight had hemiparesis, 13 bilateral spastic paresis, one athetosis, three ataxia, and seven belong in the mixed group.

E. CLINICAL CONSIDERATIONS

Early diagnosis.

The early *diagnosis of cerebral palsy* is difficult.
During the first years of life the nervous system of a child is immature. The movements of the normal infant are neurologically primitive and aimless. He kicks his feet alternately, and he opens and closes his fists. Normally he lies with his back curved when in a resting position. All his reflexes are primitive: searching for the breast in response to stimuli to the cheeks, the sucking reflex, "extensor thrust" of the tongue, the tonic neck reflex, Moro reflex, grasping reflex of the fingers and toes are the most important ones.

The brain-injured baby may show a rigidity which is rarely seen in the normal infant. Suggestive of brain lesion are a persistent opisthotonous position, failure of the child to open his hands spontaneously, or his lying with stiff legs, never kicking. Difficulties in sucking and swallowing often occur in brain-injured children, but in babyhood cannot be considered of diagnostic importance, since the symptom may also be due to other causes. If it persists, however, it becomes more significant.

As pointed out by Craig and others, these early symptoms suggestive of brain injury may disappear and the patient may grow up without clinically demonstrable sequelae.

When three to five months old, the reflex grasping of the hands normally should loosen, and the child should begin to grasp voluntarily. At that age the spastic and rigid patient will make no effort to grasp at all. The athetoid will try, but his movements are poorly directed. At this stage, however, making a distinction from the primitive movements of the healthy child is difficult.

During the second half-year of life the impulse of the child to voluntary grasping becomes more distinct. In the case of cerebral palsy, the observant mother may say of her child at that age: "He is trying to grasp, but he can't make it".

The typical athetoid movements of the fingers and toes usually are not observed before the age of one and a half to two years. Until then they are incoordinate, but look more ataxic than athetoid.

In the course of the second year of life, muscular tonus deviations become more diagnostically significant.

Spasticity in the usual sense, as demonstrated in spastic stretch reflex, is not seen in the infant. The development is gradual, and the symptom may not be recognised before the age of two or three years. Children who later have spastic paresis or extrapyramidal symptoms, during the first one or two years of life usually show "lead-pipe"rigidity.

According to Collis (1954) there are two early signs of spasticity. If a child, who later develops spastic paresis, is held by its feet, head down and one foot is let go, that leg remains stiffly out sideways, whereas in a normal child it will drop down in flexion at the hip and knee joints. If the leg is pushed down in flexion, it straightens to its former position. Adductor spasm in the hip also is an early symptom, usually observed considerably before the appearance of spastic stretch reflex in arms and legs.

When a new-born child is lifted and supported from under the stomach, its head falls down and its back curves. At the age of one to three or four months, the child should be able to keep his head lifted, and when six to eight months old, he should learn to sit unsupported. Persistent lack of strength beyond the physiological time is suggestive of cerebral injury.

However, prolonged observation and additional symptoms are needed to decide the degree and type of the lesion.

Some infants with marked hypotonia later develop athetosis or ataxia, and according to Collis (1954) and Ingram (1955) rigidity sometimes occurs.

Before the age of two or three years, the differential diagnosis between athetosis and ataxia is difficult.

Hemiparesis is the type of cerebral palsy which can be the earlier diagnosed, when of moderate degree. Mild cases may escape notice during the first months of life, but when the child is eight or nine months old, the mother of such babies usually notices that they use only one hand, or that the use of the other hand is extremely clumsy. As for the legs, the demonstration of a mild one-sided paresis may be difficult before the child begins to walk. In hemiparesis, differences in the reflexes, those on the affected side being more lively, are usually found.

In spastic diplegia, examination of the deep reflexes has relatively small diagnostic value in infancy. Normally they are livelier and the reflexogenic zone wider than in adults. The plantar reflex normally may be inverted up to the age of three years or more.

An early differential diagnosis between cerebral palsy and *mental deficiency* is difficult. Both conditions may cause retarded motor development. In cerebral palsied patients the primitive reflexes should disappear at the normal time. Collis (1953) claims the disappearance or persistence of the primitive reflexes to be an important differential diagnostisticum between cerebral

palsy and mental deficiency. Persistence indicates severe mental defect. This agrees with the author's own experience regarding all the primitive reflexes, with the possible exception of the grasp reflex of the hands. In spastic paresis an apparent persistence of the grasp reflex up to the age of one year, may actually be due to increase of muscle tone. A clinical distinction may be difficult or impossible.

The movements of a child mentally impaired may appear to be involuntary, and twitchings of the fingers may suggest athetoid movements. On close inspection, however, the movement pattern in the mentally defective is seen to be harmonious.

Cerebral palsy and mental deficiency often coincide. In such cases the relative importance of the motor disorders and the mental condition to the retarded development can only be decided after prolonged observation, and especially by the patient's response to treatment.

In the course of the second year of life, the diagnosis of cerebral palsy should be possible for the experienced physician.

Many authors make the diagnosis of cerebral palsy dependent on *non-progression of the condition.* In such an evaluation the maturation of the central nervous system throughout babyhood and infancy must be considered. Just as determination of involuntary movements is impossible before the child has reached the physiological age for voluntary movements, neither is an ataxic gait estimable before the child should have a normal gait, according to its age and mental development. An intimate knowledge of the development of a normal child, and particularly of the range of the normal variations, is necessary for the evaluation of a brain-injured child.

It has been claimed (Bronson Crothers 1953) that in some patients proliferation of the glial cicatrical tissue may occur and give clinical symtoms not corresponding to the primary cerebral lesion alone.

Crothers believes this to be a possible explanation of a progression of the clinical symptoms. He describes a few patients with good recovery from pyramidal defects, who on re-examination after ten years showed aggravation with increasing signs of extrapyramidal involvement. No such case has occurred in this study, but the observation time was short.

Classification of the Clinical Types.

In hardly any field of cerebral palsy research has greater difference of opinion prevailed than in the grouping of the various manifestation forms. This may be explained by the multitude of variations in the neurological picture in cerebral palsy. The early authors, from Freud to Phelps, classified

the patient preferably according to the extremities involved, and whether it was most pronounced in the arms or the legs. The categories of their classification were: hemiplegia, diplegia, paraplegia, and double hemiplegia. The nature of the affection, whether spasticity or athetosis-chorea, was of secondary importance.

Phelps (1941) set up the following groups based on the types of affection: Spasticity, athetosis, tremor, ataxia, and rigidity. His definition of spasticity is: "Where in one or more regions on the patient's body a muscle gives spastic stretch reflex, that patient is a spastic". In the athetosis group he includes all forms of involuntary and incoordinate movements, tremor and ataxia excepted. He listed twelve athetosis subgroups (Lectures at the cerebral palsy congress in London, autumn 1954. His own explanations).

1. Rotation athetoid	–	"Hand and shoulder rotate, no tension".
2. Tremor-like group		
3. Dystonic athetoid	–	"Usually with tension".
4. Shudder athetoid	–	"They shudder involuntarily".
5. Flail-like athetoid	–	"Big movements, weak muscles, no tension".
6. Hemiathetoid	–	
7. Neck and arm athetoid	–	"Good legs".
8. Tension-athetoid	–	"Temporary diagnosis, the tension masks the other group".
9. Non-tension athetoid	–	"A child so limp you cannot tell which group it is".
10. Deaf-athetoid or Rh-athetoid		
11. Balance-athetoid	–	"Rare group. They walk as on a train in movement".
12. Emotional release group	–	"Rare fits of laughing, crying, rage etc.".

Tremor, rigidity, and ataxia Phelps classifies as separate groups, and the frequency he gives at 5 % to 6 % of all cases. He believes mixed forms to be rare.

Since Phelps published the principles of his classification, these have more or less, with some variations, been the most used in the work with cerebral palsy.

Collis (1945) gives a somewhat divergent definition of athetosis: "Distorted voluntary movements".

She explains her view:

"The term athetosis is often used to describe any incoherence or incoordination of movements irrespective of its origin, and this is confusing because there is no other diagnostic term to distinguish this last group (pure athetosis) from the others (cases of athetoid movements with rigidity and mental defects). For lack of diagnostic term for these cases, we have restricted to them our use of the term athetosis. In them the sole abnormal characteristic of physical activity is generalized, unsteadiness of movements, including that of speech, and this abnormality must be distinguished from the incoherence of movements associated with mental defect . . ., as well as from ataxic type of incoordination".

Collis gives a detailed description of the patients whom she includes under "rigidity" (Arch. Dis. Child 1954). She claims never to have found rigidity without simultaneous severe mental defects. In many cases the movements of these patients are incoordinate, so pronounced as often to be described as athetoid. The motor characteristics may change with age, constant rigidity become intermittent, and some infants who display slight rigidity may gradually develop severe degrees. Many of these patients have ankle clonus (Collis).

Ford (1952) divided the spastic pareses into hemiplegias, diplegias, bilateral hemiplegias, and monoplegias. The extra-pyramidal syndromes he divided into congenital double athetosis, congenital double chorea, congenital rigidity, cases with atypical movements, cases of involuntary movements complicated by spasticity and other symptoms. Of the latter groups he declares: "There are several syndromes originating in intrauterine life which are usually attributed to defects of the basal ganglia of the forebrain. All of these present disorders of muscle tone and in most instances involuntary movements as a prominent feature. The classical syndromes are connected with one another by transitional cases and others are complicated by signs of disease of the pyramidal tracts so that a great variety of clinical pictures are possible".

Perlstein's classification (1955) is as follows:

1. Spastics—due presumably to pyramidal tract involvement. These are characterized by stretch reflexes, increased muscle tone and the classical finding of "upper motor neuron" involvement. This group makes up 68 % of the total.
2. Dyskinesias—due presumably to extrapyramidal tract involvement.
   a. Athetosis: Characterized by involuntary, incoordinate, uncontrollable, purposeless movements with varying degrees of muscle spasm or tension. This group makes up 22 % of the total members of c.p.

b. Dystonics: Characterized by marked tension with greater involvements of the axial muscles and resultant postural attitudes.
c. Tremors: Characterized by uncontrollable motions, pendular or pattern like in nature, involving alternate agonist–antagonist muscle actions.
d. Rigidities: Characterized by a resistance to slow passive motion, which is usually intermittent, and by simultaneous contractions of agonist and antagonist muscle groups.

3. Ataxias: Presumably due to involvement of cerebellum and its tracts (5 %).
Ataxia and spasticity usually occur as pure syndromes. The various subtypes of the dyskinesias frequently coexist with one of them exhibiting intermittent and variable predominance.

In the various classifications neither the degree of mental defect nor the sensory losses are considered. Apart from the reduction of deep sensibility and posture sense in ataxia, on the whole the sensory losses in cerebral palsy have been little studied. The reason is probably partly a lack of interest, as no gross changes occur in the senses of touch, pain, and temperature, and partly the difficulty of demonstrating finer sensory losses in infants. The interest is growing, however.

Some authors (Bronson Crothers et al.) have found sensory losses especially in hemiplegia, and reduced joint sensibility especially in bilateral spasticity in a not inconsiderable number of cases. In the present study the examination for finer sensory disorders has not been systematic.

Thus it is apparent that the classification of the clinical types of cerebral palsy is rather diverse, and the differential diagnosis within the subgroups often difficult and tentative. The distinction between tension and rigidity in a patient with athetoid movements may be extremely difficult, and the diagnosis requires prolonged observation. Tension, described by Phelps as a defence mechanism against involuntary movements, is reduced after relaxing exercises, while rigidity will persist. Phelps and others believe tension in athetosis to be "superimposed", the patient tightening his muscles to resist the involuntary movements produced by all strong or unexpected impulses. In untreated cases the muscles finally will be in a chronic state of tension, and the patient stiffen into distorted positions. The evaluation of such cases, whether spastic, athetoid, or rigid, is very difficult. Determination of the plantar reflex in the athetoid may be nearly impossible because of strong warding-off movements. These patients often suffer from subluxation of the hip joints.

Rigidity in children with cerebral palsy differs from that in adults as it is often intermittent and varying. At times the child may be so stiff that passive bending of the limbs is difficult. At other times he may be found to be completely relaxed. A change in the position may influence the degree of rigidity. The child himself seems absolutely without control of the condition.

Determination of the type is particularly difficult in the very young and in old neglected cases.

The delineation of the clinical types is not clear cut. From the recent advances in the knowledge of the anatomy and physiology of the brain, this is not surprising. Considering the demonstrated anatomical-physiological intimate relationship between the pyramidal and the extra-pyramidal systems, and that lesions at many different sites may give similar symptoms, the former sharp distinction between losses from the two systems can hardly be maintained. In the present study determination of the types was often difficult. The differential diagnosis is the easiest in the pure forms of spasticity with spastic stretch reflex, increased tendon reflexes, and a positive Babinski sign. These patients were classified in two groups: spastic hemiparesis and spastic diplegia. The athetosis and ataxia groups include all cases of unmixed athetosis and ataxia respectively.

In contrast to Phelps and Perlstein, the author is of the opinion that a great number of patients cannot be definitely classified into any of these groups. Many patients showed losses both from the pyramidal and the extra-pyramidal system. Some had ataxia in addition to pyramidal and/or other extra-pyramidal symptoms. Further, a number of patients offered the picture of choreo-athetotic movements plus marked rigidity. Six showed rigidity without involuntary movements or symptoms from the pyramidal tract, and in five pronounced hypotonia was the only demonstrable neurologic symptom.

For practical reasons all these patients have been collected into one group, called "Mixed group". Clinically all were severe cases with defective intelligence more marked than in the rest of the cases.

The mixed group of the present study includes the following clinical types:

51	patients	13.8 %	both pyramidal and extra-pyramidal losses.
15	"	4.1 %	rigidity + involuntary movements.
6	"	1.6 %	rigidity the only symptom.
5	"	1.3 %	hypotonia the only symtom.
6	"	1.6 %	ataxia + pyramidal and/or extra-pyramidal sympt.
		22.4 %	

The following table shows the relative frequency of the various clinical types:

Table 14.

	Patients—Total number	%	Spasticity % Total	Hospital-patients	Out-patients	Classification (%) of Out-patients
Hemiparesis R.	51	13.8		14	37	19.4 %
Hemiparesis L.	38	10.3	56.7	11	27	14.1 %
Bilateral spasticity	121	32.7		59	62	32.5 %
Athetosis	53	14.3		31	22	11.5 %
Ataxia	24	6.5		7	17	8.9 %
Mixed group	83	22.4		57	26	13.6 %
Total	370			179	191	

The classifications in some other studies are given for comparison.

	Phelps	Nilsonne	Asher/ Schonell	Scheel/ Thomsen
Number of cases	350	375	349	118
Spasticity	54 %	72 %	83 %	77.1 %
Athetosis + chorea	40.9 %	23	10	9.3
Spasticity + athetosis			5	4.2
Rigidity		2.5	0.3	0.9
Ataxia	5.1	2.5	1	6.8
Other forms			0.7	1.7

Pneumoencephalographic Findings.

Pneumoencephalography (PEG) was done on 105 of 370 patients. Apart from the first two years of the period, the material does not represent selected cases. During the last three years all patients had the examination, if not contraindicated by factors such as young age, fever, poor general condition, and if it was not objected to by the parents. For 79 patients PEG was successful

and permitted evaluation of the ventricular system. All interpretations and evaluations were made by Sigurd Eek, who gives the following criteria for the normal pneumoencephalogram (personal information 1955):

"The ventricular system should be symmetrical, third and fourth ventricle situated in the mid-line.The two lateral ventriclesshould be of equal size and found at the same distance from the mid-line on the two sides. The upper lateral corner of cella media of the lateral ventricles should be acute-angled. The distance of the caudate nucleus contour from septum pellucidum (the mid-line) should in anterior view be the same on both sides, and have the characteristic S-shape. A difference in the distance over 2 mm. from the mid-line on the two sides is considered pathological. Maximal anterior width of third ventricle is considered normal in children when measuring under 6 mm. A width of 6-8 mm. is suspect of pathologic dilatation, and when over 8 mm. it is definitely pathological. With a distance over 18 mm. from floor to fastigium in the fourth ventricle it is considered dilated. Maximal width of the two temporal horns in anterior view, should not exceed a couple of mm. With a width over 5 mm., it is highly suspect of pathologic dilatation. On a difference in the width of the temporal horns over 2 mm. in the same projection, the wider one is considered pathological. The conditions of the basal cisterns and sulci are not estimable by exact measurement. The basal cisterns normally vary in shape and size. The sub-arachnoidal air over the cerebral hemispheres gives anatomical informations of the sulci. Neither here can the exact metric dimensions be given. However, the sulci should be quite narrow, and when air-filled they should appear in the roentgenogram as fine linear clearings."

The number of PEG examinations in the different groups appears in

Table 15.

Type		Total no. of patients	PEG		
			Normal	Pathologic	Unsuccessful
Hemiparesis	Right	51 (24 %)	1	8	0
	Left	38	0	7	0
Bilateral spasticity		121 (33 %)	7	21	11
Athetosis		53 (14 %)	2	7	6
Ataxia		24 (7 %)	1	1	1
Mixed group		83 (22 %)	2	22	8
Total		370 (100 %)	13 (16 %)	66 (84 %)	26

According to the above criteria 16 % of the successful pneumograms are normal, 84 % pathological. The following findings are considered to be pathological: Dilatation of the ventricular system, dislocation of the ventricles from the normal position, and increased width of sulci on the cerebral surface.

The degree of dilatation in the pathologic PEG is divided into four groups: Slight–moderate–severe–and extremely severe changes. The distribution of these groups is seen in Table 16.

Table 16.

Degree of Dilatation in the Pneumoencephalogram.

Types		I	II	III	IV
		Slight changes	Moderate changes	Severe changes	Extremely severe changes
Hemiparesis	Right	0	4	3	1
	Left	0	4	1	2
Bilateral spasticity		2	2	11	6
Athetosis		3	2	1	1
Ataxia			1		
Mixed group		2	9	9	2
Total		7 (10 %)	22 (33 %)	25 (38 %)	12 (19 %)

The following tables give the patients' clinical type, sex, age, and the most important PEG and EEG findings in these patients.

It appears that organic changes in the brain, so considerable as to be demonstrable in PEG, occur in 84 % of the cerebral palsy patients. The pathologic changes observed are on the whole of two types:

1) Changes found in spastic hemiparesis.
2) Changes found in all the other clinical types.

Table 17.

Pneumoencephalographic Findings in Right-sided Hemiparesis.

Pt. No.	Sex	Age years	Pneumoencephalographic findings	Degree*)	Site of changes	I.Q.	Electroencephalography
1	Female	6	General cerebral lesion, most on left side.	II	Bilateral	79–71	–
2	Male	2	General cerebral lesion, most on left side Sulci dilated bilaterally.	II	Bilateral	–	–
3	Female	5	Local, cortical left-sided lesion.	II	Unilateral	–	Normal.
4	Male	5	Normal.	–	–	–	Marked reduction on left side. Epileptogenic focus in parietal region.
5	Female	2	General cerebral lesion, most on left side. Dilated sulci on right side.	III	Bilateral	–	Left-sided cerebral dysrhythmia.
6	Female	1	Severe left-sided lesion. *Porencephalia.*	IV	Bilateral	Idiot	Considerable reduction over left hemisphere.
7	Female	7	Severe dilatation of left lateral ventricle, probable dilat. of right lateral ventricle.	III	Probably bilateral	–	Epileptogenic focus in left temporal region.
8	Male	1	General central and cortical lesion.	III	Bilateral	–	Considerable general dysrhythmia. Epileptogenic focus in left temporal region.
9	Female	1	Retractive left-sided process. Large third ventricle.	II	Probably bilateral	–	General dysthrythmia. Epileptogenic focus in left occipital region.

*) I: Slight changes. II: Moderate changes. III: Severe changes. IV: Extremely severe changes.

Table 17 cont.

Pneumoencephalographic Findings in Left-sided Hemiparesis.

Pt. No.	Sex	Age years	Pneumoencephalography	Degree	Site of changes	I.Q.	Electroencephalography
1	Male	1	General cerebral lesion, most on right side.	II	Bilateral	–	Right-sided focal cortical dysrhythmia.
2	Male	3	Dilated right cella media + right ant. horn, and normal temp. horn.	II	Unilateral	–	Dysrhythmia over whole of right hemisphere. Epileptogenic focus in r. temp. oceip. region.
3	Female	2	Cortical lesion in left frontal region. Sulci on right side not air-filled. Normal ventricular system.	II	Unilateral	Idiot	Epileptogenic focus in right hemisphere + bilateral synchronous spike-waves.
4	Male	3	Asymmetric ventricular system. Right-sided retractive process.	II	Unilateral	–	Epileptogenic focus in whole of the right hemisphere.
5	Female	1	Enormous dilatation of the entire ventricular system, and severe cortical lesion.	IV	Bilateral	Under 50	Epileptogenic focus in whole of the right hemisphere.
6	Male	2	General cerebral lesion, most on right side + *Porencephalia.*	III	Bilateral	72	Right-sided reduction. Epileptogenic focus in right hemisphere.
7	Male	2	Considerably dilated ventricular system most on right side. Large third ventricle. Severe dilat. of sulci on left side.	IV	Bilateral	Under 50	Epileptogenic focus in right hemisphere.

Table 17 cont.

Pneumoencephalographic Findings in Bilateral Spastic Forms of Cerebral Palsy.

Pt. No.	Sex	Age years	Pneumoencephalography	Degree	I.Q.	Electroencephalography
1	Male	9	General cerebral lesion, most on right side.	III	85—80	Slight general dysrhythmia.
2	Female	4	Considerable general lesions.	III	88—90	Normal.
3	Male	8	Severe general lesion.	IV		General dysrhythmia.
4	Male	3	Right-sided lesion. Wide sulci on right side. No air in sulci on left side.	I	Idiot	—
5	Male	4	Hypoplasia and right-sided *Porencephalia.*	IV	—	Slight general dysrhythmia.
6	Male	10	General cerebral lesion, mostly central.	II	90—100	Slight general dysrhythmia.
7	Male	11	Considerable general cerebral lesion.	IV	Under 50	Slight dysrhythmia, focal left-sided.
8	Female	3	Central cerebral lesion.	II	Normal	—
9	Male	2	General cerebral lesion.	IV	Normal	—
10	Female	5	General cerebral lesion. Sept. pellucidum cyst.	III	114	Normal.
11	Male	3	Severe pathologic changes. *Porencephalia.*	IV	50—60	—
12	Female	3	Central cerebral lesions. Normal sulci.	III	80	Normal.
13	Female	7	General central cerebral lesion.	III	—	Normal.
14	Male	6	Normal.	—	116	Slight general dysrhythmia.
15	Male	4	Normal.	—	90—96	Normal.

Table 17 cont.

Pt. No.	Sex	Age years	Pneumoencephalography	Degree	I.Q.	Electroencephalography
16	Male	5	Normal.	–	100	Normal.
17	Male	2	Normal.	–	112	Normal.
18	Male	6	Normal.	–	88	Normal.
19	Female	7	Normal.	–	–	Normal.
20	Male	5	Severe central lesion, most on left side.	III	98	Slight general dysrhythmia.
21	Female	3	Dilatation of left cella media. Large third ventricle. Normal left temporal horn.	I	103	Normal.
22	Female	3	General cerebral lesion, most on left side.	III	Under 50	Focal dysrhythmia in anterior part of right hemisphere.
23	Male	2	Severe general lesion.	IV	–	–
24	Male	4	Pronounced general cerebral lesion.	III	Idiot	–
25	Male	1	Severe general cerebral lesion.	III	Idiot	–
26	Female	5	Considerable cerebral lesion, most on left side.	III	84	Epileptogenic foci bilaterally.
27	Male	5	Cerebral lesion around third ventr. and around left temp. horn.	III	Normal	General dysrhythmia. Epileptogenic foci bilaterally.
28	Male	6	Normal.	–	Under 50	Numerous bilateral synchronous spikes.

Table 17 cont.

Pneumoencephalographic Findings in Athetosis.

Pt. No.	Sex	Age	Pneumoencephalography	Degree	I.Q.	Electroencephalography
1	Male	8	Bilateral and central cerebral lesion. Normal sulci.	II	75	Normal.
2	Male	4	Normal.	–	50	–
3	Male	3	Normal.	–	Normal	Normal.
4	Female	1	General cerebral lesion, most on left side.	III	–	Normal.
5	Male	10/12	General central and cortical lesion.	I	–	Normal.
6	Female	8	Retractive process lateral to right cella media. Large basal cisterns.	I	81	Normal.
7	Male	2	Considerable general cerebral lesion.	II	–	Slight general dysrhythmia.
8	Male	8	Lesion in right hemisphere. Dilated third and fourth ventricle. Large basal cisterns. Normal sulci.	I	85–90	Slight general dysrhythmia.
9	Male	9	Bilateral cerebral lesion.	IV	80	Bilateral synchronous spike-waves.

Pneumoencephalographic Findings in Ataxia.

Pt. No.	Sex	Age	Pneumoencephalography	Degree	I.Q.	Electroencephalography
1	Male	7	Central cerebral lesion, specially around fourth ventricle.	II	86	Slight general dysrhythmia.
2	Male	10	Normal	–	–	–

Table 17 cont.

Pneumoencephalographic Findings in Mixed Forms of Cerebral Palsy.

Pr. No.	Sex	Age	Pneumoencephalography	Degree	I.Q.	Electroencephalography
1	Male	4	General cerebral lesions. Sulci dilated on right side.	II	Idiot	Normal.
2	Male	1/2	General cerebral lesion with considerable cortical changes.	IV	Idiot	–
3	Male	1	General cerebral lesions, most on left side.	III	–	–
4	Male	2	General cerebral lesions, normal sulci.	III	Under 50	Normal.
5	Female	16	General central lesions.	II	80	Slight general dysrhythmia.
6	Female	10	General central cerebral lesions.	III	Idiot	–
7	Male	10	General central cerebral lesions.	II	55	General dysrhythmia.
8	Female	13	General central cerebral lesions. Normal sulci. *Partial agen. corpus callosum.*	III	60–70	General dysrhythmia.
9	Female	8	General central cerebral lesions.	III	Under 50	–
10	Male	3	General central cerebral lesions, most on left side.	II	Under 50	–
11	Male	2	General central cerebral lesions.	III	Idiot	–
12	Male	1	General central cerebral lesions.	III	–	Normal.
13	Female	7	General cerebral lesions, most in left frontal region.	I	40	Right-sided focal dysrhythmia.

I: 2 patients. II: 2 patients. III: 9 patients. IV: 2 patients.

Table 17 cont.

Pneumoencephalographic Findings in Mixed Forms of Cerebral Palsy.

Pt. No.	Sex	Age	Pneumoencephalography	Degree	I.Q.	Electroencephalography
14	Male	3	Normal.	–	–	Normal.
15	Male	3	Normal.	–	Under 50	Normal.
16	Male	7	Left-sided cerebral lesions. Large basal cisterns. Normal sulci.	I	Normal	Normal.
17	Male	2	Left-sided temporal lesion.	II	–	Slight general dysrhythmia.
18	Male	11	Retractive cerebral lesion in right temporoparietal region. Normal sulci.	II	80	Normal.
19	Male	3	General central cerebral lesion, most on left side.	III	Idiot	Slight general dysrhythmia.
20	Male	4	General central cerebral lesions, most on left side.	II	Under 50	Epileptogenic focus in left central region.
21	Female	1	General cerebral lesion.	II	–	–
22	Male	2	General cerebral lesion.	II	Under 50	–
23	Male	1	General cerebral lesions, most on left side.	III	Under 50	Slight left-sided dysrhythmia.
24	Female	7	General central lesion. Normal sulci.	IV	–	General dysrhythmia. Epileptogenic focus in right occipital region.

I: 2 patients. II: 2 patients. III: 9 patients: IV: 2 patients.

Group 1.

In 15 of the 16 hemiparetics PEG was pathological. In 14 the findings consisted of dilatation of the lateral ventricles, principally of the cella media of these structures. In 10 there was simultaneous dilatation of the third and fourth ventricle (8 and 3 patients respectively).

It is worth noting that in 11 of the 14 patients the changes were *bilateral*, if distinctly *asymmetrical*, with the greater changes on the side opposite the hemiparesis. In three only the dilatation was unilateral, and contralateral to the hemiparesis. In one patient the pathologic finding was ipsilateral. This was the only case in the material with a normal ventricular system, and where PEG showed only cortical lesion. Here pronounced atrophy in the left frontal region was found (Patient No. 3, left-sided hemiparesis), and no air in the sulci on the right side. The patient was severely mentally defective, and had epileptogenic foci in the right hemisphere.

To draw conclusions from these findings with regard to the pathologic changes in the separate cases is hardly possible. The roentgenograms that showed dilatation, especially of the cella media of the lateral ventricles, might suggest that in spastic hemiparesis the pathologic changes in the motor region of cortex are most pronounced contralaterally. Dilatation of the third and fourth ventricle might be read as an indication of deep central changes. However, these conclusions must be regarded with considerable reserve.

Group 2.

The hemiplegias are the only types of cerebral palsy which give a characteristic PEG and the only ones for which PEG may suggest the probable diagnosis. In all other varieties of the disease, PEG is strikingly uniform and permits no conclusions regarding the clinical type.

In the great majority of cases, dilatation was found in the central and lateral ventricles. In most cases, the changes were practically of equal degree on both sides. A few showed some asymmetry. Dilatation of the third ventricle was marked in the picture of all the clinical types. It was seen in 41 patients, sometimes to a very severe degree.

11 patients also had dilatation of the fourth ventricle, but in 19 the fourth ventricle was not air-filled.

In 44 cases of the total PEG material, the air over the cerebral surface permitted an evaluation of the sulci. In 9 the condition was found to be normal, in 35 the shape of the sulci was pathological. Of the latter, 34 also had pathologic dilatation of the ventricular system. One patient only showed pathologic condition of the cerebral surface and a normal ventricular system. This case already has been mentioned (No. 3, left-sided hemiparesis).

In cerebral palsy, the hemiplegias excepted, PEG shows mainly deep-

seated central dilatation of the ventricular system. This applies to patients with spastic diplegia as well as to those with extra-pyramidal symptoms. Thus, in spastic paresis there is often considerable dilatation of the third and fourth ventricles. An exception of some interest is the case of an athetoid in whom PEG showed: Retractive process lateral to the right cella media, possibly an indication of cortical atrophy in the motor region.

The involvement in the bilateral forms of cerebral palsy of a process which principally strikes *centrally, localized to the basal nuclei and the adjacent parts of the pyramidal tracts*, seems an obvious conclusion. The area might correspond to that supplied by Vena Galeni magna. Whether this is the only or main location of the pathologic process is not known. Even though the possibility cannot be excluded, it seems hardly probable that the uniform roentgenologic picture could be due to congenital malformations in the brain. It would be more reasonable to presume that the demonstrated dilatations were the result of atrophic cerebral changes from acquired injuries.

The following conclusion seems justified:

1) The roentgenologic findings are not incompatible with deep-seated cerebral birth injuries as the main cause of the disease.
2) If so, the pneumoencephalographic findings are in accordance with the previously mentioned theory of the etiology of cerebral palsy.

In 13 of the 79 patients the pneumoencephalographic findings were normal. 6 of the 13 were clinically mild cases of spastic paraplegia with normal intelligence. One patient with spastic diplegia was mentally impaired. Three showed sequelae after kernicterus. Two had athetosis and one athetosis plus rigidity. One had uncomplicated ataxia and one ataxia plus rigidity. The last case was a right-sided hemiplegia. The finding of a normal PEG in this patient seemed rather strange, since EEG showed marked reduction of the electric cerebral activity over the whole of the left hemisphere.

Table 18.

PEG in relation to I.Q.

I.Q.	Number of patients	PEG normal	PEG pathologic			
			I	II	III	IV
Under 50	23	2	2	5	9	5
50–85	14	1	1	5	5	2
Over 85	17	6	3	3	4	1
Not tested	25	4	1	9	7	4
Total	79	13	7	22	25	12

Among the patients who had PEG examination there was a relative preponderance of mentally impaired. The reason for this is partly that only hospital patients were thus examined, and partly that during the first two years of the period, only the more mentally defective had the tests.

Although the numbers are too small to permit definite conclusions, Table 18 suggests an existing correlation between mental impairment and pathologic PEG findings. Only three of 37 patients with I.Q. under 85 showed normal findings, while normal PEG was found in six of 17 with normal mental endowment. Further, there seems to be some predominance of severe PEG findings among the mentally impaired children.

The Pneumoencephalographic Findings in Relation to Epilepsy and to a Pathologic EEG.

23 of the 79 patients who had pneumoencephalographic examination (PEG) also had epilepsy. In 22 of these, PEG was pathological, often with marked changes. For only one patient did the examination give negative results (see Table 19).

Table 19.

Pneumoencephalographic Findings.

Cerebral palsy with epilepsy	Total number of patients	PEG normal	Pathologic PEG			
			I	II	III	IV
Hemiparesis R.	7	1		2	3	1
Hemiparesis L.	6			3	1	2
Spasticity	4 (+3)	(1)			3 (2)	1
Athetosis	1					1
Ataxia	0					
Mixed group	5 (+1)			3	2	(1)
Total	23	1		8	9	5

In addition there were four patients without manifest convulsions, but in whom EEG revealed spike foci (in brackets).

EEG was made of 49 patients with pathologic PEG. In 15 it was found to be normal, 12 showed slight focal or general dysrhythmia, and 22 had markedly pathologic EEG.

For comparison, Table 20 presents *the pneumoencephalograpic findings in 167 patients with epilepsy without other neurological symptoms.*

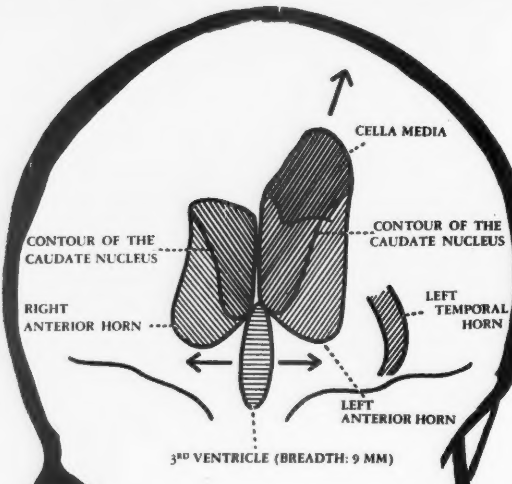
Table 20.

Normal	Pathological				Total
	Degree I	II	III	IV	
67	21	39	32	8	167

The pathologic PEG findings were strikingly like those found in cerebral palsy. The lesions were mainly central or central plus cortical, of the same appearance and extent as the changes that occur in cerebral palsy.

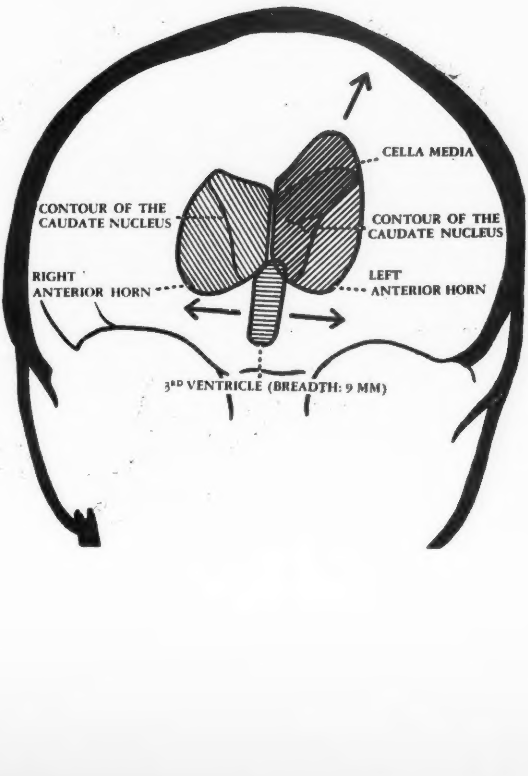
Hemiparesis R.
Patient no. 1.

(Table p. 37)



L. side ventricle dilated, especially cella media and temporal horn. Marked dilatation of third ventricle.

Hemiparesis R.
Patient no. 1.
(Table p. 37)



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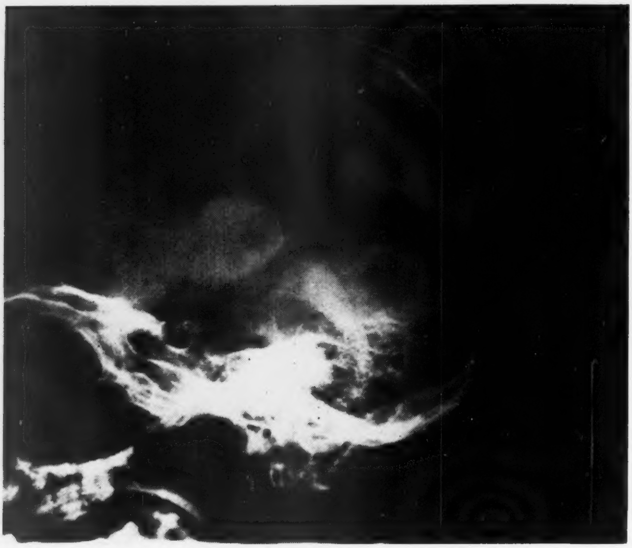
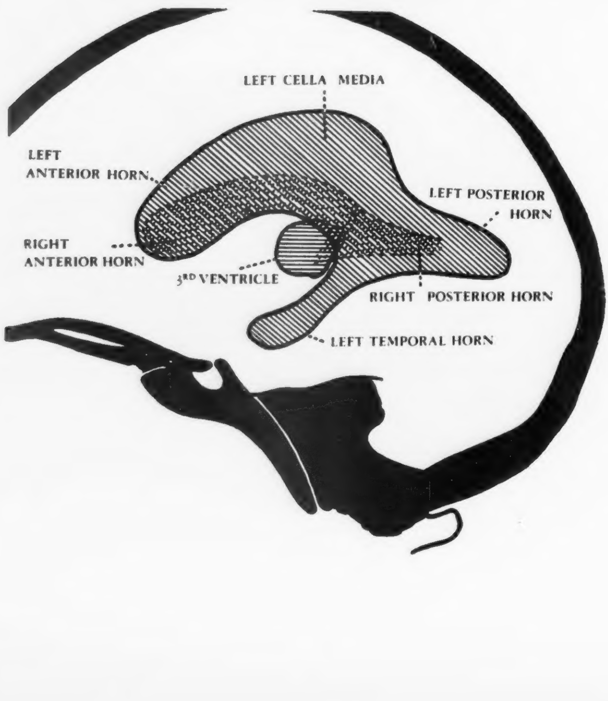
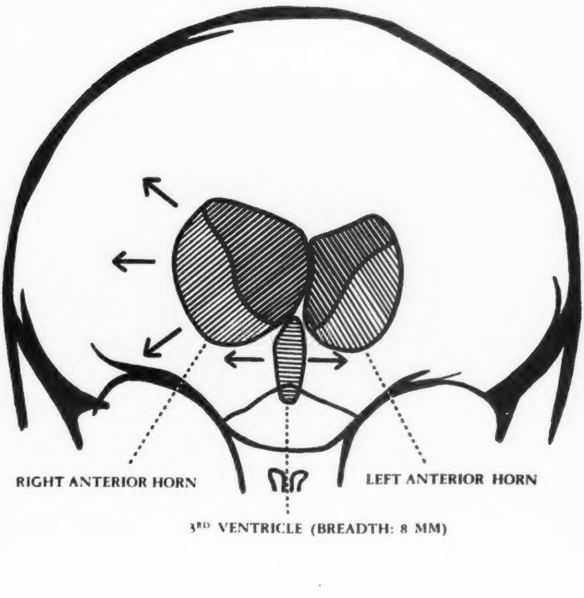
Hemiparesis R.
Patient no. 1.
(Table p. 37)

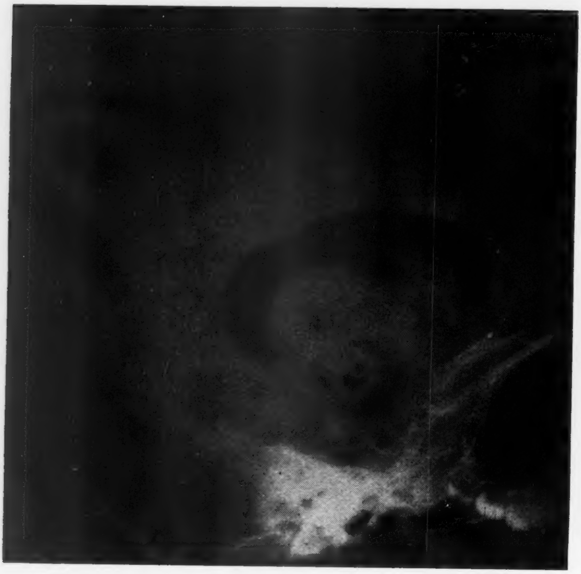




Hemiparesis L.
Patient no. 1.
(Table p. 38)

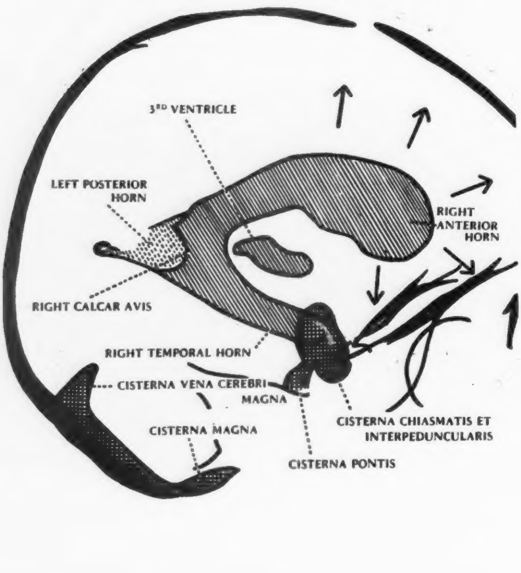


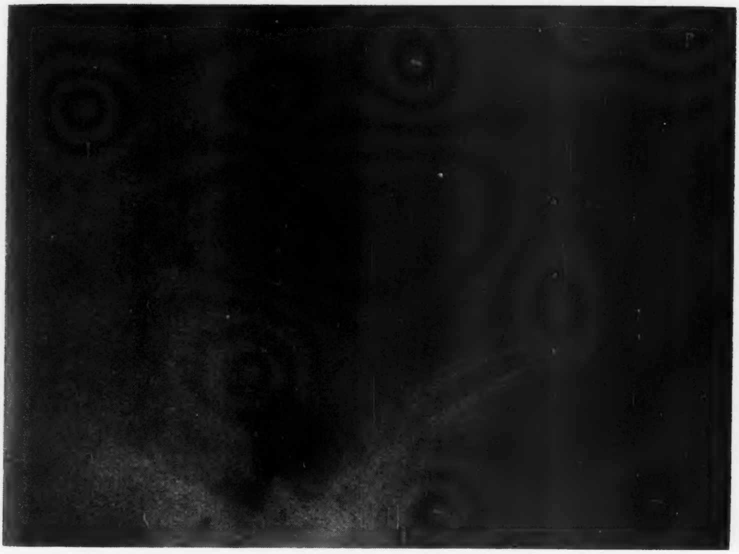
General dilatation of ventricle system, especially R. side. Large basal cisternae. Large cisterna magna.

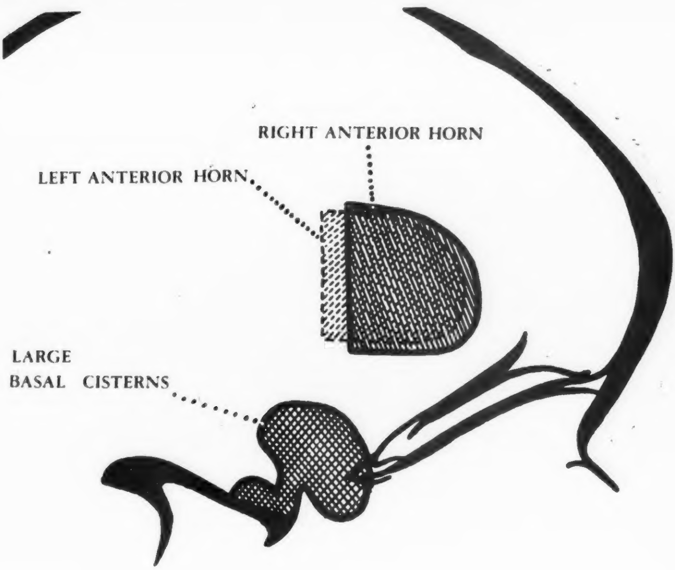


Hemiparesis L.
Patient no. 1.
(Table p. 38)

Hemiparesis L.
Patient no. 1. →






RIGHT ANTERIOR HORN
LEFT ANTERIOR HORN
LARGE
BASAL CISTERNS

Bilateral spastic paresis. Patient no. 2.

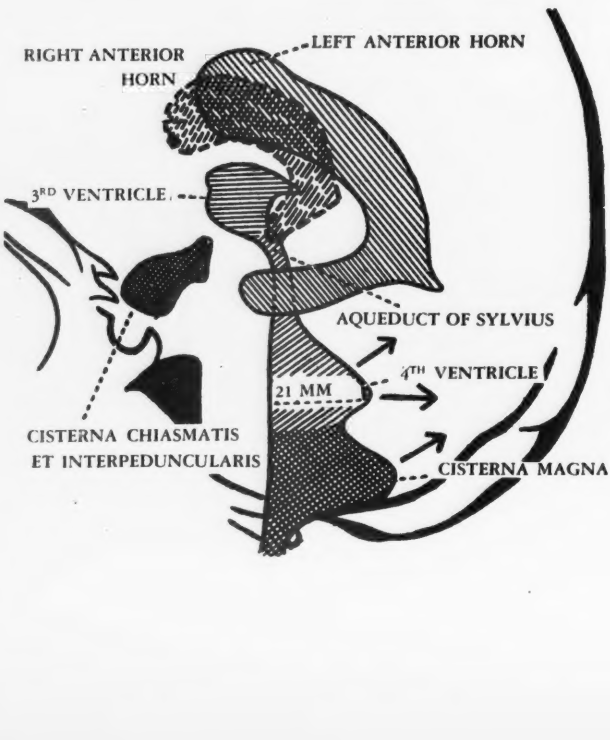
(Table p. 39)

Side ventricles and temporal horn normal. Third and fourth ventricles dilated.

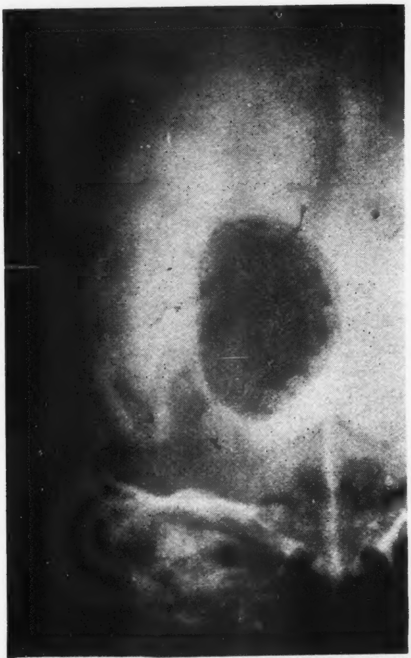
Bilateral spastic paresis. Patient no. 2.
(Table p. 39)

Bilateral spastic paresis. Patient no. 2.

(Table p. 39)



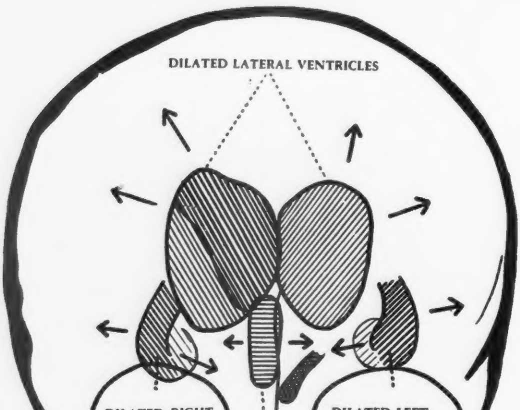
Athetosis.
Patient no. 9.
(Table p. 41)

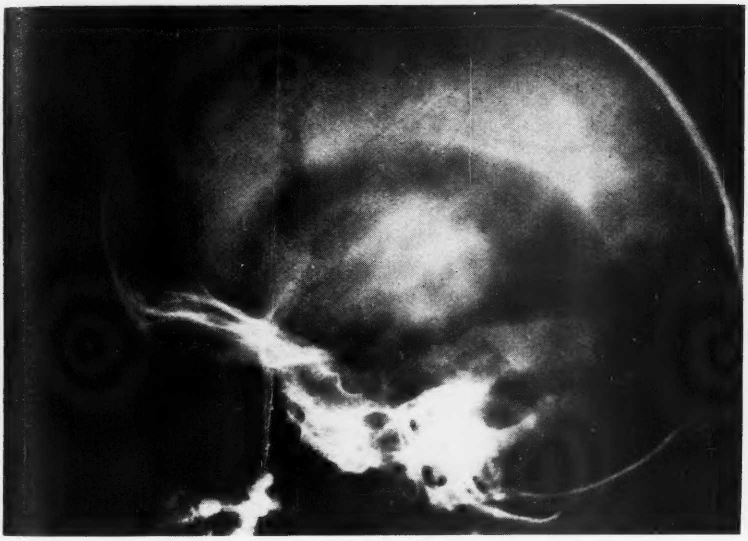


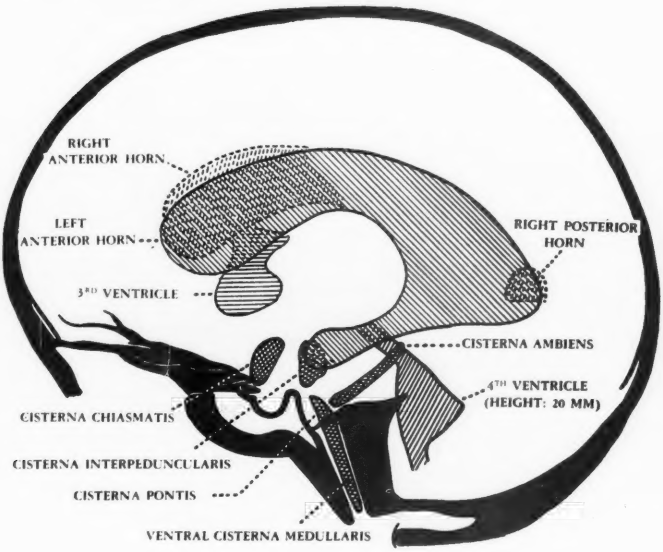
Both side ventricles and temporal horn dilated. R. side ventricle larger than L. Dilatation of third and fourth ventricles. Large basal cisternae.

Athetosis.
Patient no. 9.
(Table p. 41)

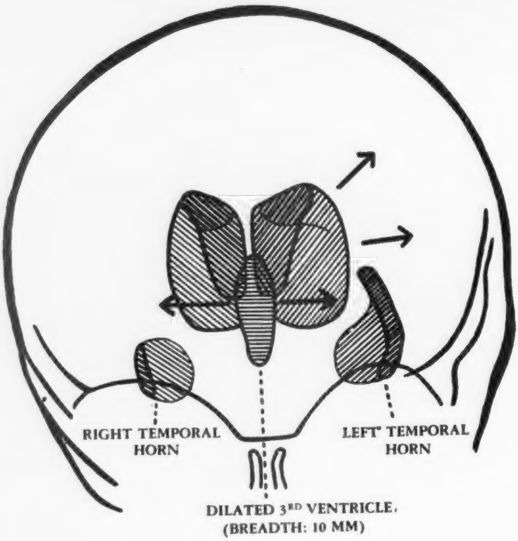
Patient no. 9.
Athetosis.





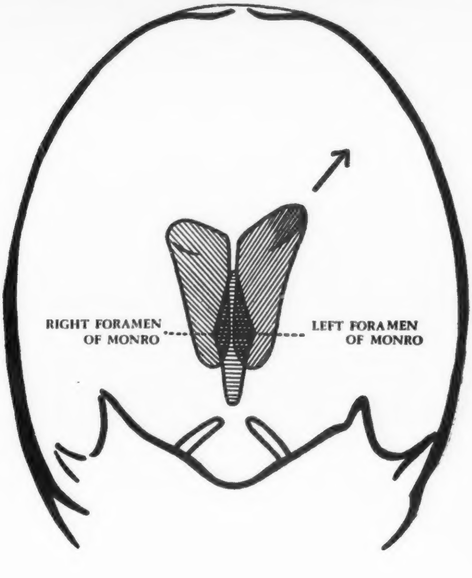

RIGHT
ANTERIOR HORN
LEFT
ANTERIOR HORN
RIGHT POSTERIOR
HORN
3RD VENTRICLE
CISTERNA AMBIENS
4TH VENTRICLE
(HEIGHT: 20 MM)
CISTERNA CHIASMATIS
CISTERNA INTERPEDUNCULARIS
CISTERNA PONTIS
VENTRAL CISTERNA MEDULLARIS

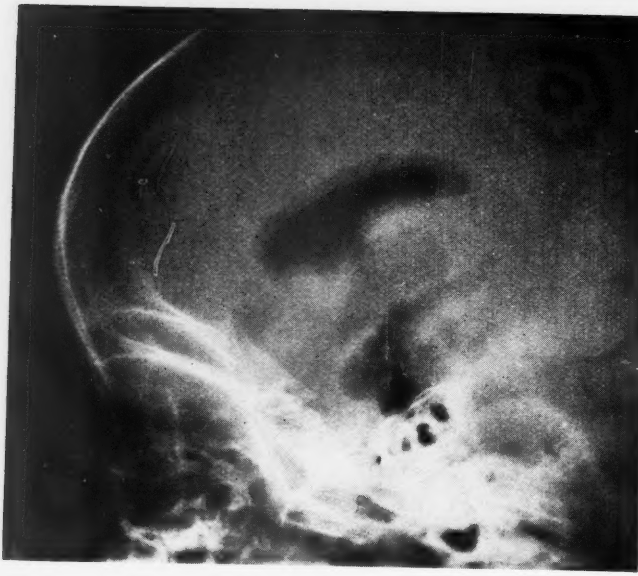
Mixed group.
Patient no. 12.
(Table p. 42)



Upper lateral horn of R. side ventricle slightly rounded. Considerable dilatation of third ventricle, somewhat less of fourth ventricle. Wide sulci.

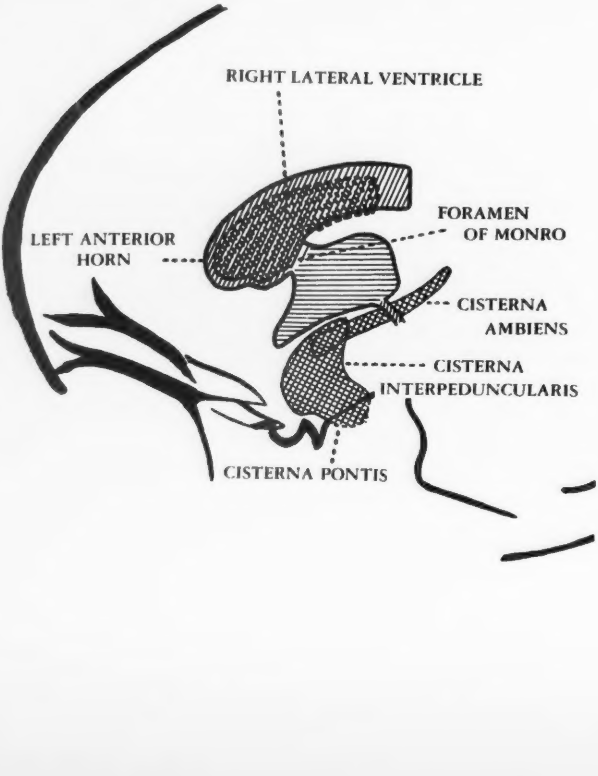
Patient no. 12.
Mixed group.
(Table p. 42)





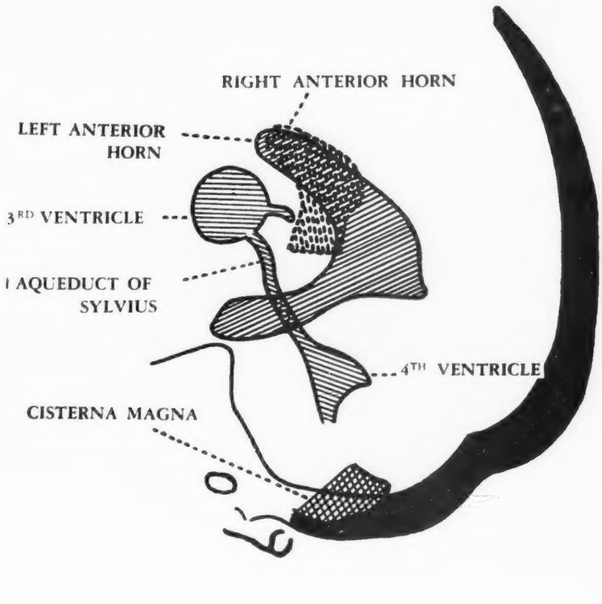
Mixed group. Patient no. 12.

(Tab'e p. 42)

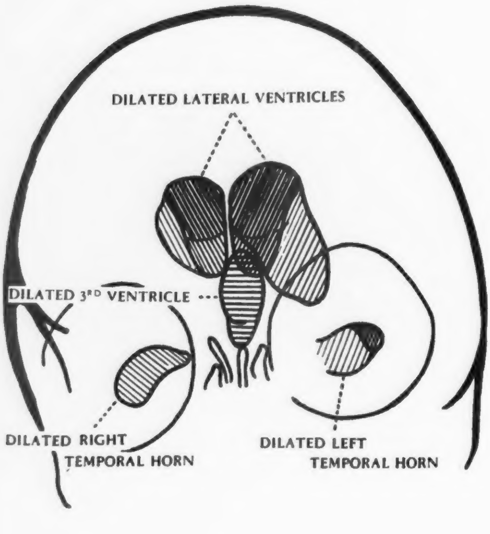


Mixed group. Patient no. 12.

(Table p .42)

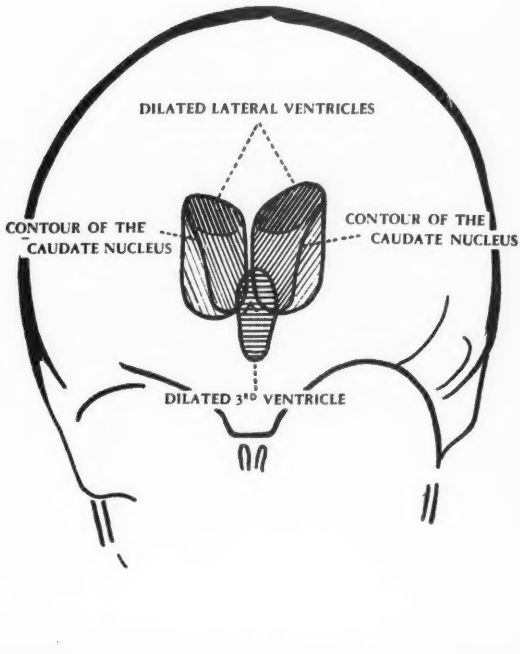


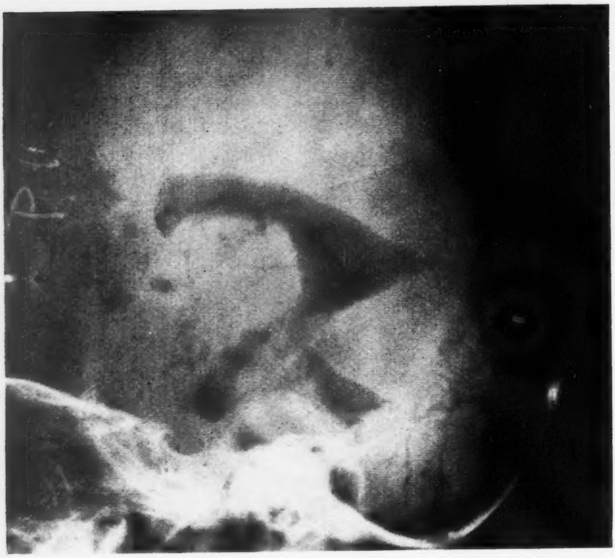
Epilepsy without cerebral palsy.



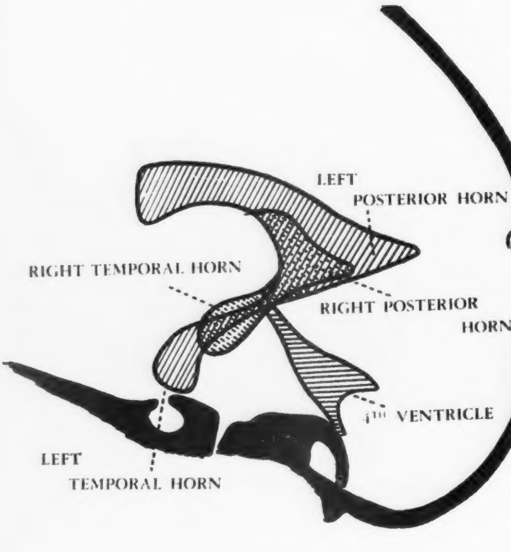
Slightly dilated L.side ventricle. Marked dilatation of L.temporal horn. Third ventricle much dilated (width 11 mm). Fourth ventricle normal.

Epilepsy without cerebral palsy.





Epilepsy without cerebral palsy.



Other Defects often Associated with Cerebral Palsy.

Limiting the concept of cerebral palsy to the motor symptoms alone would be to consider only one part of the syndrome. In addition to the motor disorders, other symptoms may occur with varying frequency. The most important ones are *mental impairment* and *epilepsy*.

Cerebral palsy, mental deficiency after cerebral injury, and organic epilepsy logically can be considered as a pathologic entity, often of the same origin. The extent and location of the cerebral lesion apparently decide whether the result be a microcephalic idiot with hydrocephalus e vacuo, some form of cerebral palsy, an organic epileptogenic focus, or combinations of these conditions.

Of interest in this connection is the previously mentioned amazing likeness between the PEG findings in cerebral palsy and in epilepsy without other neurological symptoms.

Mental Deficiency and Cerebral Palsy.

The question of the patient's real intelligence is a major one in all work with cerebral palsy. Because of their lack of stability, their involuntary movements, grimacing, and drooling, their mask-like faces, speech disturbances, and auditory and visual defects, the cerebral palsy patients formerly were generally considered to be mentally defective. Then Phelps' famous work appeared, wherein he claimed that about 70 % of the patients are normally intelligent, or sufficiently for the child to be educable. The optimism that followed has now been somewhat dampened.

In late years the technique of testing has been considerably improved, and methods have been worked out for the estimation, not only of I.Q., but of other mental qualities as well.

However, it is evident that testing of these children presents great difficulties. There are factors which may cause errors of judgment. Benda pointed out that for the performance of a test, higher intelligence is required of a cerebral palsied child than of a normal one, who knows how to move and express himself. Another error factor is a tendency in the examiner to seek too good a result, ascribing mistakes to the handicap of the child, whereas actually defective intelligence is the cause. In spite of these difficulties, the various intelligence tests reported, Phelps' excepted, show quite good correlation.

Table 21.

I.Q.	Phelps	Burgemeister and Blum (1949)	Asher and Schonell (1950)	Miller (1952)	Nilsonne (1952)	Holoran (1952)	Ingram (1955)
					Under 75		
Under 70	31 %	53 %	49 %	50.0 %	48 %	39.0 %	43.8 %
					Over 75		70—84
70—90	69 %	47 %	27 %	22.5 %	52 %	36.2 %	24.2 %
							Over 85
Over 90			24 %	27.5 %		24.8 %	32.0 %

Edith Meyer and Bronson Crothers (1953) report 80 cases which they examined and re-examined after 10 years. Edith Meyer declares: Only a few of the patients have "high average intelligence", and even these nearly without exception show "demonstrable distortions in mental functioning". At the re-examination few appeared socially and sexually adapted, and none held an occupation with mentionable responsibility. "They are not normal, and should not be regarded as normal".

M. S. Dunsdon (England 1952) found an I.Q. over 100 in only 6.3 % of 368 applicants to special schools for cerebral palsy patients. More than half the number was mentally subnormal. It may be objected, however, that the mild cases with presumed normal intelligence would not be among the applicants to these special schools.

Most authors find the intelligence relatively less reduced in athetosis and ataxia, most in rigidity. An exception is Asher and Schonell, who found the average intelligence about equally reduced in the various types, in spasticity an average I.Q. of 67.9, in athetosis 67.6, and in ataxia 62.3, Asher and Schonell show a parallelism between the degree of physical and mental defects. They found a mean I.Q. of 81.8 in the slight degrees of motor disturbance, 71.7 in moderate degrees, 55.6 in severe cases, and 24.6 in the most severe.

As mentioned, 212 patients of the present material had intelligence tests. All those examined were over two years old.

The results are rather in agreement with those reported in Table 21, albeit with a somewhat higher intelligence level. Normal intelligence (I.Q.) over 85) was found in 43.9 %; in 34.4 % it was low enough to prevent education in ordinary schools and to reduce cooperation in physical therapy to a minimum (I.Q. under 50).

Table 22.

I.Q.	Normal	50—85	Under 50	Total
Hemiparesis R.	5	2	3	10
Hemiparesis L.	5	3	4	12
Bilateral spasticity	46	18	16	80
Athetosis	23	8	0	31
Ataxia	10	6	2	18
Mixed group	4	9	48	61
Total	93	46	73	212

Normal I.Q. (over 85)	43.9 %
50–85	21.7 %
Under 50	34.4 %

The author is aware that the above figures should be regarded with some reservation. The test results for the cerebral palsy patients generally show a wide range. Numerical specification of the I.Q. as an average of the many answers therefore may be misleading.

However, in the author's opinion, the results as a whole express the actual situation. The number of mentally impaired in the material may even be thought rather high, as most of the 212 tested were hospital patients. For practical reasons many of the out-patients with apparently normal intelligence could not be tested.

Among the cases studied, the intelligence is relatively the highest in the athetoid and the lowest in the mixed group. Of the latter group, only four patients were within the limits of normal intelligence, as against 23 of 31 of the athetoids. In the other groups, about 50 % were found of normal intelligence. No certain difference was demonstrable between the bilaterally and the unilaterally affected. The number of hemiplegia patients examined is too small, however, for definite conclusions in this respect. In accordance with Perlstein's studies of hemiparesis (1955), the present study shows no difference in the I.Q. between the right- and the left-sided hemiplegias. The number of cases is small, however. As mentioned, some relation apparently exists between the degree of intelligence reduction and that of the PEG changes.

The conclusions to be drawn from the examinations with regard to the therapeutic results are as follows:

Well over one-third of the cerebral palsy patients must be cared for in

institutions for the mentally defective. Physical therapy may save them from stiffening into distorted positions, but no social improvement can be expected. Well over 20 % are more or less educable and may be more or less benefited by therapeutic treatment.

43 % of the patients had normal mental endowment and should be entitled to extensive therapy. In Norway there should be *about 1000 patients under 21 years old* within the category.

The Electroencephalographic Findings and Epilepsy in Cerebral Palsy.

Few works have appeared on EEG examinations in cerebral palsy.

Perlstein, Gibbs, and Gibbs (1946) examined 212 cerebral palsy patients of the spastic and athetoid types. They found the percentage of pathologic EEG considerably higher in the spastics than in the athetoids. Of 86 spastics with epilepsy, EEG was normal in 5 %, "Mildly abnormal" in 11 %, and "Very abnormal" in 84 %. For spastics without convulsions (56 cases) the corresponding numbers for normal were 41 %, for slightly pathological 26 %, and for severely pathological 33 %. Of 12 athetoids with convulsions EEG was normal in 33 %, slightly pathological in 25 %, and severely pathological in 42 %. Of 58 athetoids without convulsions, EEG was normal in 73 %, slightly pathological in 17 %, and severely pathological in only 10 %. In 27 % of the spastics without manifest clinical seizures they found seizure discharges.

Aird and Cohen (1950) made EEG examination of 187 cerebral palsy patients aged one to twenty-one years. 128 were spastics, 53 athetoids, and six "other types". They found pathological EEG in 85 % of the spastics and in 60 % of the athetoids. Of these cases focal dysrhythmia occurred in 62 % of the spastics and in 32 % of the athetoids. The number of pathologic EEGs was somewhat higher in the severe than in the moderate clinical forms of spasticity, but not of athetosis. Eighty-three of their spastics and eighteen athetoids had convulsions. Eighty-eight per cent of the spastics and sixty-one per cent of the athetoids had pathologic EEG.

As mentioned, (p. 4), EEG was made on 223 patients. All were registered at the Neurological Department's EEG Laboratory of the Rikshospital, and described by the medical staff of the laboratory, most of the cases by Georg Henriksen and Arne Lundervold. The following analysis is based on their reports. An 8-channel Kayser electroencephalograph was used, with both mono- and bipolar leads.

Table 23.

Number of EEG Examinations within the Different Groups.

	Total number EEG	Whereof	
		Normal	Pathologic
Hemiparesis R.	35	7	28
Hemiparesis L.	20	1	19
Bilateral spasticity	72	37	35
Athetosis	35	15	20
Ataxia	15	5	10
Mixed group	46	23	23
Total	223	88	135
		39.4 %	60.6 %

The pathologic EEG has been divided into focal dysrhythmias, general dysrhythmias, bilateral synchronous spikes, and spike-waves.

Table 24.

	Focal dysrhythmias			General dysrhythmias		Bilateral synchronous spikes and or spike—waves
	Right side	Left side	Bilat-eral	Severe—moderate	Slight	
Hemiparesis R.		22	2	4 (3)	2	3 (2)
Hemiparesis L.	16		2	1 (1)	1	1 (1)
Bilateral spasticity	8	4	5	3 (1)	12	4
Athetosis	1	6	1	1 (1)	10	2
Ataxia	2	0	1	1	6	
Mixed group	4	3	4	10 (5)	6	2 (1)
Total	31	35	15	20	37	12

The focal dysrhythmias consist partly of theta-delta waves, spikes, sharp waves, spikes and waves, or focal reduction of the normal cerebral electric activity, partly of combinations of these forms.

Registered as bilateral dysrhythmias are cases which partly show isolated epileptogenic foci in both hemispheres (spikes and spike-waves), partly reduced cerebral activity or theta-delta activity in the one hemisphere and epileptogenic foci in the other.

Nine right-sided and seven left-sided hemiparetics showed reduced cerebral

activity, in all contralateral to the hemiparesis, while one bilateral spastic, one athetoid, but no ataxic or patient in the mixed group, showed reduced cerebral activity in EEG. In two with left-sided hemiparesis, epileptogenic foci were found in the left hemisphere, but both patients had "considerable destruction of function in the right hemisphere". One of these had had encephalitis, the second was mentally impaired.

In the group "severe to moderate general dysrhythmias" the figures in brackets represent patients who in addition to general dysrhythmias had epileptogenic foci, and therefore belong in both groups. Likewise, in the group "bilateral synchronous spike-waves" the figures in brackets give the number of patients in whom EEG showed both bilateral synchronous spike-waves and focal spikes.

In no cases did the bilateral synchronous spike-waves show the classical 3/sec. spike-waves, and no patient in the material had classical "petit mal" seizures.

In 37 patients (about 17 %) EEG showed only slight general dysrhythmia, in 88 (39.4 %) EEG was normal.

The fact that EEG gave no pathologic finding in such a high percentage of these manifestly brain-injured children may at a first glance seem strange. In the clinically most severe group, the mixed one, 50 % showed nothing pathologic. It should be kept in mind, however, that only cells with pathologic activity give dysrhythmias. And as is known, it takes a rather large area of dead cells to produce the picture of reduced cerebral activity. Scattered minor foci of dead cells will not appear in EEG. Besides, EEG series are not available for all the patients. Further, development of an epileptogenic focus often occurs several years after the primary cerebral injury.

Otherwise, good correlation was observed between EEG and the clinical findings. In the hemiparetics dysrhythmia was usually contralateral, in the other groups it was found to be scattered, partly focal, partly general.

Epilepsy in Cerebral Palsy.

All authors agree that epilepsy is a frequent complication of cerebral palsy.

Brochway (1936) found epilepsy in 18 % of 1000 cerebral palsy patients, and in 39 % of the hemiparesis cases.

Asher and Schonell (1950) reported the occurrence of epilepsy in 23.8 % in spastic quadriplegia, in 24.2 % in spastic hemiplegia, in 3 % in spastic paraplegia, and in 4 % of the athetoids.

Perlstein (1954) found convulsions in 43 % of 324 hemiparesis cases.

In a recent publication (August 1955) Perlstein, Gibbs, and Gibbs give a

greater frequency of epilepsy in a large cerebral palsy material. Of 1217 patients, 47 % had convulsions. Of the spastics, the paraplegias excepted, 63 % had convulsions, of spastics of the paraplegia type 33 %, of dyskinetic patients 22 %, of the ataxic 20 %. Included are also patients with convulsive twitchings in the neonatal period, convulsions during fever, even cases with a single seizure.

Accurate determination of the frequency of epilepsy in the present study was not possible. The evaluation to a great extent had to be based upon the parents' statement that their children had had repeated convulsive seizures. Therefore, inclusion of fever convulsions or other non-epileptic forms of seizures may have occurred.

Cases of convulsions in the neonatal period are not included, nor are those with seizures during an encephalitis (two cerebral palsy patients who have had no seizure since, and who had normal EEG two years after the illness). Otherwise all cases of convulsions were counted.

Eighty-two of the 370 patients had manifest convulsions. With the above reservation, this showed epilepsy in 22 %. The frequency within the various clinical types of cerebral palsy appears in Table 25.

Table 25.

	Number of patients who have had manifest convulsions	Number of patients with convulsions and no EEG registration	Convulsions and no epileptogenic foci in EEG		Epileptogenic focus in EEG without manifest convulsions	Epileptogenic focus in EEG with manifest convulsions	Total number of patients in the material	% of convulsions in the separate groups
			EEG normal	EEG pathological				
Hemiparesis R.	18	2	1	1	7	14	51	34.8 %
Hemiparesis L.	13		1	3	1	13	38	
Bilateral spasticity	23	10			8	9	121	19.0 %
Athetosis	4	1			5	3	53	7.5 %
Ataxia	3	1	1		2	1	24	12.5 %
Mixed group	21	7	3	5	4	6	83	25.3 %
Total	82	21	6	9	27	46	370	22.0 %
			15					

The table shows considerable variations in the frequency of epilepsy within the various clinical types. They are the most frequent in spastic hemiplegia with 35 %. The mixed group and bilateral spasticity hold an intermediate position with 25 % and 19 % respectively. The incidence is the lowest in the purely extrapyramidal types (ataxia 12.5 %, athetosis 7.5 %).

Of the 82 patients with convulsions, 61 had EEG examination. In six of these, EEG was normal (one recording only), 46 had one or more epileptogenic foci, nine had pathologic EEG without epileptogenic foci.

Twenty-seven of the patients examined in EEG (223 patients) had spike foci without manifest convulsive seizures within the period of the present work (until September 1955).

Whether the demonstrated spike-foci in the 27 patients indicate later epileptic seizures in the these cases is not yet clear. Gibbs, Gibbs, and Perlstein (1955) declare that an answer to the question is possible only after a longer observation period than hitherto reported. For one patient in this study, the possibility seems indicated. At 16 months old, her EEG showed marked reduction of cerebral activity in the central region on the left side, no spike activity. At three years old, her EEG showed reduction in the same part and some additional sharp waves in that region. Five weeks later she had a convulsive seizure that lasted several hours. Seven weeks after the seizure, EEG showed series of spikes over the middle part of the left hemisphere.

The epileptogenic foci in 73 patients were scattered over most of the brain, with slight preference to the central and temporal regions. Twenty-three were right-sided, thirty-two left-sided, while ten had spike foci in both hemispheres. Twelve patients had bilateral synchronous spikes and spike-waves in EEG, four of whom also had cortical spike foci.

Table 26.

Location of Epileptogenic Foci.

	Frontal		Central		Temporal		Temporo—Central		Temporo—Parietal		Temporo—Occipital		Parietal		Parieto—Central		Parieto—Occipital		Occipital		Occipital—Parietal—Temporal		The whole of one Hemisphere		Bilateral Foci
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	
Hemiparesis R.		2	0	4		3		1		1				2		1		1		2				1	2
Hemiparesis L.	2	1			2	1					1				1		1					2	3		
Bilateral spasticity	1			1	3								2	1					1					1	3
Athetosis		1		2		1														1					1
Ataxia			1								1														1
Mixed group				2									1						2		1				3
Total	7		10		10		1		1		2		6		2		2		6		3		5		10

Table 27.

Location of Epileptogenic Foci in Relation to the Patient's Age.

Location of focus	0—5 yrs	5—10 yrs	Over 10 yrs	Total
Frontal	3	4	1	8
Anterior temporal	1	1		2
Central	4	7	1	12
Posterior temporal	4	4	2	10
Temporo-parietal	1			1
Temporo-central		2		2
Temporo-occipital	3			3
Parietal	4	2	1	7
Parieto-central	3			3
Parieto-occipital	3			3
Occipital	5	1		6
Occipital-parietal-temporal	1	1	1	3
Epileptogenic activ. over one entire hemisph.	4		1	5
Bilateral synchronous spike-waves	4	3	1	8

Gibbs and Gibbs (1954) claim the location of the epileptogenic foci to have some relation to the patient's age. In the young they usually occur in the posterior part of the brain. Gibbs gives occipital foci as the most common in children about 4 years old, and the mid-temporal region in the nine-year old.

Gibbs' assertion finds support to some extent in the present study. In the great majority of patients, especially in children about five years old, the epileptogenic foci were found in the posterior region.

The central region considered anterior, eight patients under five years had epileptogenic foci in the anterior, as against twenty-two in the posterior location. When only the frontal and anterior temporal regions are considered anterior (Gibbs), the tendency becomes even more pronounced. This gives four anterior and 26 posterior locations in those under 5 years old. The finding of the mid-temporal region as the most common location of epileptogenic foci in children about nine years, is not confirmed in the present study. Here this location is found in only six of twenty-two patients aged between five and ten years.

"Shift of focus" in children has been described by Gibbs and Gibbs (1954) and Lundervold and Skatvedt (1956).

In the present study, which includes only to a small extent electroencephalographic serial examinations throughout a prolonged period of time, the location of the epileptogenic foci has changed in two patients.

One had spastic diplegia. At the age of four years his EEG showed isolated spikes in the occipital region. On re-examination when 6½ years old, the previously demonstrated spikes in the occipital region were not found, while EEG showed spikes in the left posterior temporal and in the right parietal region. One year later (April 1955) no spikes appeared in the EEG record. The patient had had anti-epileptic treatment the whole time, and no seizures had occurred during the last three years.

The second patient, an ataxic, had had focal theta-delta activity with sharp waves in the right temporo-occipital region at the age of two years. When 5½ years old her EEG showed epileptogenic focus in the right anterior temporal region. Up to the present time (September 1955) this patient has had no manifest epileptic seizures.

Etiological Factors in Cerebral Palsy Patients with Epilepsy. (Manifest Convulsions.)

Heredity: In the case of five of the 82 patients (5.9%) convulsive seizures were reported in relatives. The relationship in the five cases was: one mother, one brother, one paternal grandmother, one maternal aunt, and one paternal aunt.

For comparison it may be mentioned that in a material examined by the author, consisting of 360 patients aged 0 to 14 years, with epilepsy and no cerebral palsy, convulsive seizures in relatives were reported in a total of 27.8 %, and in the near family—parents, grandparents, brothers and sisters—in 7.8 %.

No special difference was observed between the cerebral palsy patients with epilepsy and the rest of the cases as regard disturbances during the maternal pregnancies.

Among the cerebral palsy patients with convulsions, 39 (47.5 %) had pathologic birth. The corresponding number for all the cerebral palsy cases was 43.8 %.

Thirty patients in the convulsion group (36.6 %) had symptoms of asphyxia/cerebral hemorrhage in the neonatal period. For the total number of cases the corresponding number was 47 %.

Nineteen of the children with convulsions (23.2 %) were prematures

(birth-weights under 2500 gms). Prematurity in the total study was 28.2 %. Six of the former (well over 7 %) had birth-weights over 4000 gms, in the total material 15.5 %.

Among the 82 patients with convulsions, 7 (8.5 %) had postnatal meningitis/encephalitis, as against 3.2 % in the total material.

A comparison between these numbers for birth-weights and the corresponding values for the above material of epileptics without cerebral palsy is interesting. Among the latter, the prematurity rate was considerably lower (9.5 %), while the number of large children (over 4000 gms) was higher (24 %). In the simple epilepsy cases the birth was pathologic for 21.7 %, and 15.6 % had had symptoms of asphyxia/cerebral hemorrhage.

Conclusion: With regard to the etiological factors, the difference between cerebral palsy patients with and without epilepsy is slight. The relatively frequent occurrence of meningitis/encephalitis may possibly indicate a somewhat greater tendency to epilepsy development in these patients. The numbers are too small, however, to permit definite conclusions.

However, the rather considerable difference between *simple epilepsy cases* and those of epilepsy in cerebral palsy is interesting as regards some possible etiological factors. In simple epilepsy, familial occurrence of convulsions is far more frequent. The importance of neonatal injury to cerebral palsy and concurrent epilepsy seems indicated by the more frequent occurrence of prematurity, pathologic birth, and clinical symptoms of asphyxia/cerebral hemorrhage in these patients than in those with epilepsy alone.

Intelligence Quotient in Cerebral Palsy Patients with Epilepsy.

51 of 82 patients were tested.

Table 28.

	I.Q. under 50	I.Q. 50—85	Normal I.Q. over 85	Total
Hemiparesis R.	3	1	3	7
Hemiparesis L.	4	2	2	8
Bilateral spasticity	7	2	5	14
Athetosis		1	1	2
Ataxia		2	1	3
Mixed group	15	2		17
Total	29	10	12	51

As already mentioned, the relative frequency of children within the three intelligence groups (I.Q. under 50, 50–85, over 85) in the total material was 34.4 %, 21.7 %, and 43.9 % respectively.

Table 28 shows I.Q. to be considerably lower for the cerebral palsy patients with, than for those without manifest convulsive seizures. 29 of 51 (57 %) belong in the group of the lowest intelligence. 12 only (24 %) had normal I.Q. The finding is particularly marked in the mixed group, where none of the 17 children tested had normal intelligence.

A possible explanation of the findings might be that the presence of convulsions in cerebral palsy indicates a more severe degree of the disease. But no definite conclusion can be drawn.

Clinical Reflections on Cerebral Palsy Patients with Epilepsy.

Table 29 gives the age of the patients at the time of the manifestation of convulsions. (Twitchings in the neonatal period, if not persisting, are not included).

Table 29.

Age at the first seizure	0—6 months	6 months to 1 year	1—2 years	2—4 years	4—6 years	6—10 years	Over 10 years	Total
Hemiparesis R.	1	3	4	6	2	1	1	18
Hemiparesis L.	3	1	2	4		1	2	13
Bilateral spasticity	5	5		8	1	3	1	23
Athetosis	1	1	1		1			4
Ataxia	1			1	1			3
Mixed group	12	3	2	1	2	1		21
Total	23	13	9	20	7	6	4	82

In 43.9 %, convulsions started before the age of one year. In more than half the number of patients in the mixed group, seizures occurred in the first year of life. In the other clinical types the convulsions started some time during childhood.

Types of Seizures.

The types of the seizures are divided into focal ones, with focal onset, grand mal, i. e. initial loss of consciousness plus general convulsions, and "other types of seizures". The latter represent initial loss of consciousness, sometimes with tonic, but no clonic spasm, and without aura. Duration of the unconscious state varied in the individual patient. In addition, during the seizures all, sooner or later, showed chewing and swallowing movements, myoclonic jerks, akinetic falls, or similar symptoms. Four patients had "salaam convulsions". Typical automatisms were not observed. No patient had classical petit mal seizures. In 13 cases information regarding the type of the seizures was not available.

Table 30.

Type of the seizure	Focal	Grand mal	"Other types of seizures"	No information
Hemiparesis R.	13	3		2
Hemiparesis L.	10		2	1
Bilateral spasticity	7	5	5	6
Athetosis		1	2	1
Ataxia		2	1	
Mixed group	12	4	2	3
Total	42	15	12	13

The two patients with left-sided hemiparesis and with seizures registered in Group 3, both had cortical spike-foci in EEG. One had absences of varying duration, sometimes accompanied by a groaning sound. This patient was mentally defective. In the second, the seizures consisted of loss of consciousness of varying duration, and sometimes he fell down during the fit.

Information regarding the type of the seizures is less diagnostically important for infants than for adults. Young children are hardly ever able to tell about aura, and in many with focal seizures, the loss of consciousness happens so quickly after onset of the fit, as to be indistinguishable from grand mal. In those with severe mental defect, loss of consciousness may be difficult to recognize, and is generally observed only when connected with convulsions.

Information regarding the frequency of seizures before the institution of anti-epileptic treatment was obtained for 75 patients.

Table 31.

The frequency of seizures	Daily seizures	One or more per week	Interval of weeks to 1 month between seizures	Interval of several months between seizures	Interval of 1—2 years between seizures	A few seizures in all
Hemiparesis R.	4	2	3	3	1	4
Hemiparesis L.	6	1		3	1	1
Bilateral spasticity	2	3	1	2		13
Athetosis			1		1	1
Ataxia				1	1	1
Mixed group	9		2	1		7
Total	21	6	7	10	4	27

It appears that in 36 % of the patients seizures occurred daily or several times a week, while in 41.3 % they were rare, at intervals of years.

The presence of epilepsy in a cerebral palsy patient is in itself a problem with several important consequences. The treatment of the cerebral palsy in these patients has been claimed less rewarding than in those without epilepsy.

Another problem is that the physical treatment in some of these patients will induce convulsions.

In the present study, this complication has been comparatively rare. In four patients only, three with hemiplegia and one with spastic diplegia, the physical treatment had to be discontinued because convulsions occurred. In one of the hemiparetics, the seizures ceased on anti-epileptic medications after the physical treatment had been stopped. After one year without convulsions, the physical treatment was resumed and has been kept up for 1½ years on the same dose of anti-epileptics without recurrence of the seizures.

Although in these cases the physical treatment rarely has induced convulsions, the possibility is to be considered in every case. An effort is always made to bring the epilepsy under control by medications before physical therapy is started. Care is shown in application of the treatment, and the patient is constantly observed, both with regard to medications and through regular EEG recordings.

Perlstein claims epilepsy in cerebral palsy to be more resistant to drugs than in the simple forms. This observation is not confirmed in the present study. An exception is found in some mentally defective patients with severe cerebral palsy plus epilepsy, to whom all treatment is of little avail.

Table 32 gives the results of the medical treatment of epilepsy in the material.

Table 32.

	No anti-epileptic treatment because of scant seizures	No anti-epileptic treatment because of mental deficiency	Treated with anti-epileptics			
			No seizure for over 1 year	Improved	No effect	No control
Hemiparesis R.	4		6	5		3
Hemiparesis L.	1		4	5	2	1
Bilateral spasticity	13		5	3	2	
Athetosis	1		2	1		
Ataxia	2					1
Mixed group	7	5	3		3	3
Total	28	5	20	14	7	8

The 28 who had no anti-epileptic treatment had few seizures, and had had none for several years before they arrived for treatment for their cerebral palsy. The 20 without seizures are regularly controlled and the observation periods are from one to five years. The group "Improved" includes two patients with observation times less than one year from the time of the last seizure. In the remaining 12 patients, the seizures have become milder and less frequent, but have not completely disappeared. The group includes one hemiparetic who is unable to tolerate physical treatment.

Of the seven patients in whom anti-epileptic treatment had no effect on the convulsions, four were severely mentally defective. Two of these died in status epilepticus. Patient No. 5 also died in status epilepticus. One patient had hemiparesis after encephalitis, and he still has seizures in spite of all possible combinations of anti-epileptic therapy.

Eight patients were discharged from the hospital and anti-epileptic medications ordered, but have not returned for re-examination. Three of these had severe mental deficiency.

C o n c l u s i o n: In 28 patients, epilepsy was so slight that therapy was not found to be indicated. Twelve were so severely mentally defective that treatment of their epilepsy was unessential to their cerebral palsy. In only 43 patients, i. e. about half the number, the epilepsy represented a complication to be considered in the treatment of their cerebral palsy. In twenty of these, or slightly less than half, the convulsions ceased on routine anti-epileptic treatment. In fourteen the seizures have not completely disappeared, but the patients have improved.

A comparison of these results to cases of simple epilepsy in children from the same hospital, showed that epilepsy in cerebral palsy is found no more resistant to therapy than in the simple forms.

Of 114 patients with simple epilepsy and observation times of one to seven years, 54.4 % have no seizures. 37.7 % have improved, and in 7.9 % the medical treatment has had no effect.

The anti-epileptic treatment was the same in the two groups. Diphenylhydantion and phenobarbital preferably were used, often in combination. The last year Mysoline was used for some patients on whom the other medications had not produced the desired effect. No tridione preparation was given to cerebral palsy patients with epilepsy, but it was used to some extent for petit mal in the simple epilepsy cases.

Conclusion.

In the present examination EEG has proved a valuable supplement to the diagnostic armoury. In many cases it provides information with regard to the extent of the lesions, which is not otherwise obtainable.

If an epilepsy is to be treated lege artis, EEG is indispensable both for location of the epileptogenic foci, to some extent for the choice of medications, and for controls. EEG demonstration of epileptogenic foci in patients without manifest convulsive seizures is of therapeutic importance. Both in physical therapy and in "stress" situations some caution is required in the care of these children.

As already mentioned, epilepsy in cerebral palsy patients must be evaluated in relation to the other symptoms in the case. Where the intelligence is not too low nor the motor symptoms too severe, the therapeutic problem in epilepsy is by no means insoluble. In these cases the condition may be treated along the same lines as other epilepsies, and with about as good results. There is also evidence that epilepsy in many cases represents a cerebral lesion of essentially the same nature as in cerebral palsy (See the PEG findings).

Visual, Auditory, and Speech Disturbances in Cerebral Palsy.

Visual Disturbances.

Strabismus convergens has always been considered a characteristic symptom in Little's disease. Later other visual anomalies attracted attention. Asher and Schonell reported strabismus in 33 % with spastic quadriplegia, in 16.5 % with hemiplegia, and in 14 % with athetosis.

Among 192 cerebral palsy patients, Anne Frandsen (1953) listed "strabisme in 61, nystagmus in 12, muscular incoordination in six, poor fixation in 14, peripheral paresis in one, sequelae after conj. paresis in five, i. e. a total of 99 motor anomalies in 79 patients".

Guibor (1953) gives eye defects in 75 % of 142 children with cerebral palsy.

In this study only patients with suspected visual disorders were examined by an oculist. The following anomalies of vision and eye muscles were noted.

Table 33.

	Strabismus	Refraction anomalies	Reduced central vision
Hemiparesis R.	5		
Hemiparesis L.	8	3	
Bilateral spasticity	25	12	2
Athetosis	2	3	
Ataxia	3	2	
Mixed group	10	6	5
Total	53	26	7

One patient with right-sided hemiparesis had congenital cataract. The mother of this patient had coloboma iridis.

One patient with left-sided hemiparesis showed left-sided hemianopsia. One in the mixed group had zonular cataract and one had retinitis pigmentosa.

The refraction anomalies were: myopsias, hypermetropsias, and astigmatisms. A causative relation to the cerebral palsy in these cases seems hardly probable.

The treatment of strabismus by an oculist should be started at an early age. By occlusion treatment, glasses, and operation at the proper time, binocular vision may be obtained in a great many cases.

Guibor (1955) points out that the necessity for treating refraction anomalies and strabismus in the athetoid and ataxic children is considerably more important than in normal individuals. They depend upon vision for balance. To them the value of normal vision is inestimable.

Auditory defects.

Auditory disorders have attracted attention to increasing extent as a cause of educational difficulties in cerebral palsied children.

Auditory defects are most common as sequelae after kernicterus.

Perlstein (1953) listed reduced hearing in 40 % of cerebral palsy patients who had had kernicterus. Gerard gives 70 %.

Reduced hearing is the most frequent in athetosis. Asher and Schonell found severe reduction of hearing in 10 of 55 athetoids, as against in only three of the rest of their cases. However, they indicated a possible slight reduction of hearing in a greater number of cases.

The most common auditory defect is the so-called high tone loss. Here audition may be lowered to 40-50 decibels or more, while the low tones are well heard.

In the present study definite reduction of hearing is found in 19 patients (5 %). One had spastic paresis, 14 athetosis, two ataxia, and two were mixed types. The characteristic high tone loss was found in all.

The figure–5 %–must be considered a minimum. Attempts were made to get audiograms (Ear–Nose–Throat Department) for all patients suspected of defective hearing. The examination was unsuccessful in several cases, however, because of lack of cooperation on the part of the child.

Speech Disturbances.

Speech disorders in cerebral palsy are due partly to low intelligence, partly to dyscoordination of the muscles of respiration and speech, partly to different forms of aphasia or reduced hearing.

Dysarthria is a very frequent complication in cerebral palsy.

Asher and Schonell gave the following figures:

27 % of the athetoids were unable to speak, 25 % had severe speech disorders.

In spastic quadriplegia the numbers were 37 % and 15 % respectively, but here the speech disorders were essentially due to mental impairment.

In hemi- and paraplegia they rarely found dysarthria of severe degree. Only one case of aphasia was reported in the total number of cases.

Scheel-Thomsen reports speech disorders in 58.5 %, and in Phelps' material of 467 cerebral palsy patients Palmer (1952) found "handicapping disorders of speech and hearing in 73 %".

In the present study, speech disturbances occurred in 80 of 253 patients. The severely mentally defective and children who were too young to speak were not included.

Table 34 shows the speech disorders in the various types.

Table 34.

	Dysarthria	Total number of patients examined for dysarthria	Dysarthria %
Hemiparesis R.	2	67	10.5
Hemiparesis L.	5		
Bilateral spasticity	17	90	18.8
Athetosis	29	44	66.0
Ataxia	9	21	43.0
Mixed group	18	31	58.0
Total	80	253	31.6

The findings of this study, like others, showed the highest percentage of dysarthria in athetosis and the lowest in hemiplegia. In bilateral spastic paresis the dysarthria is relatively infrequent. The author's material included three cases of aphasia.

H. PATHOLOGIC ANATOMY

The status marmoratus in athetosis demonstrated in 1920 by Vogt and Vogt, is a well-known pathologic-anatomical finding in cerebral palsy. Well-known also are the degenerative changes in the central nuclei due to kernicterus. Otherwise, the pathologic-anatomical findings in cerebral palsy are uncertain and heterogeneous.

One of the few major autopsy descriptions available was published by Benda (1952). He reported the following:

In the severe cases of "decerebrated rigidity" which end lethally in the first year of life (four cases): Extensive cystic degeneration of the central white matter.

In purely pyramidal symptoms (seven cases): A "mantle sclerosis", a cortical encephalopathy with degenerative glial changes in cortex and the adjacent subcortical white matter and cicatrical thickening of the overlying meninges.

In mixed pyramidal–extrapyramidal symptoms, cases of spastic diplegia with athetosis (26 cases): degenerative changes in the areas of the white matter and central ganglia, the veins of which drain into the Vena Galeni and its branches.

The author does not venture a personal opinion on the correctness of Benda's findings. As mentioned before–his findings in the larger autopsy group are in good agreement with the theory of anoxia in the area as the cause of the disease, and with the frequent PEG finding of dilatation of the third ventricle in the present material. However, Benda's findings apparently have not been generally recognized. His material–patients with mental defects and simultaneous cerebral palsy–undoubtedly represents only the most severe cases of the disease. Neither are his clinical observations entirely convincing.

Towbin (1955) made post-mortem studies of 23 cases of cerebral palsy. The great majority were markedly mentally retarded. As to the etiology of cerebral palsy, in six cases he pointed to developmental defects in the brain, in six to anoxia in connection with birth, in two to kernicterus, in one to cerebral hemorrhage during birth, in one to embolism because of organic

heart defect, in one to thrombosis after head trauma, in two to toxoplasmosis, and in four to hydrocephalus, of which three followed meningo-encephalitis, the cause of the fourth being unknown. The collection represents a highly varied picture of etiological factors and of pathologic-anatomical sequelae.

The American Academy for Cerebral Palsy has started "A Brain Registry" for pathologic-anatomical study of the brains of patients who have been under close clinical observation.

Perlstein (1955) writes:

> "The Registry already has corroborated the impression that the pathologic changes in the brain in some cases are not what might have been expected on the basis of orthodox concepts. Meager morbid changes have been found in cases with pronounced clinical manifestations and contrariwise unexpected changes in asymptomatic cases. To illustrate, in 1 case of severe athetosis due to kernicterus, few changes were found in the basal nuclei, most of the changes being present in the cortical region. In another case with intermittent rigidity the primary lesions proved to be agenesis of the neocerebellum."

In the present study, autopsy has been made on six patients. All represented severe degrees of the disease. The neuro-anatomical examination of the six is made by Aa. C. Løken.

No. 1. $4^1/_2$ year old. Spastic diplegia.
I.Q. Idiot. Died from broncho-pneumonia.
Neuro-anatomical examination: Diffuse sclerosis.

No. 2. 4 years old. Spastic diplegia. Premature.
I.Q. not tested, but probably considerably reduced.
Pneumoencephalography: Dilatation of the lateral ventricles and of the third ventricle. No filling of fourth ventricle and the temporal horns. Dilatation of sulci on the left side.
The patient developed high fever, had convulsive seizures, and death occurred in spite of treatment with antibiotics and phenobarbital.
Autopsy: Hyperemia of the walls of the pulmonary alveoles, and increase of fluid in the alveoles. Otherwise negative findings. Neuro-anatomical examination: Posthemorrhagic changes in the postcentral and occipital regions, corresponding reduction or complete destruction of the cortex. Diffuse sclerosis.

No. 3. 8 months old. Rigidity plus slight athetosis. Difficult forceps birth. Birth-weight 4100 gms. Perinatal asphyxia and convulsions. EEG: Normal. PEG: Not made. Cause of death: Broncho-pneumonia. Neuro-anatomical examination: Considerable cerebral atrophy with ulegyria—most pronounced in the precentral and occipital regions on the right side. Bilateral atrophy of the lenticular nucleus. Scattered loss of nerve cells and gliosis in other basal nuclei. Sclerosis of the white matter. Hydrocephalus internus.

No. 4. 4 years old. Rigidity. Precipitate birth. Severe icterus and neonatal convulsions. EEG: Normal. PEG: General cortical and central atrophy. I.Q. Severe mental deficiency. Died in high fever from no demonstrable cause. Autopsy: General examination showed no pathologic changes. Neuro-anatomical examination: Gliosis of corpus Luysii. Moderate gliosis in the thalamic and hypothalamic nuclei, specially subpially and perivascularly. Focal loss of nerve cells in hippocampus. Reactive changes in the lepto-meninges.

No. 5. Two years old. Rigidity. Protracted birth. Neonatal convulsions that persisted after transient improvement on phenobarbital medication. EEG: Not made. PEG. Fronto-parietal and central atrophy. I.Q.: Not tested, but the patient appeared to be severely mentally impaired. Cause of death: Croupous pneumonia. Neuro-anatomical examination: Chronic lepto-meningitis with diffuse hemorrhages. Diffuse gliosis in basal structures, including hypothalamus, capsula interna, and partly thalamic nuclei.

No. 6. $2^{1}/_{2}$ year old. Athetosis plus rigidity. Premature. Birth-weight 1900 gms. Severe icterus the first 2 weeks. EEG: Not made. PEG: General cerebral atrophy, specially on the left side, most pronounced in the basal structures. Died in high fever from no clinically demonstrable cause. Spinal fluid clear, no cells.
Autopsy: Normal organs.
Neuro-anatomical examination: Slight meningeal changes.
Reactive gliosis laterally in hypothalamus.

Conclusion.

Of the above six patients, four had severe changes scattered over various brain sections. Patients No. 5 had diffuse gliosis in the basal structures. In No. 6 the findings were scarce and hardly corresponding to the severe clinical symptoms in the case.

These few autopsy findings seem to confirm the statement by Perlstein.

G. THERAPEUTIC POSSIBILITIES

Since Phelps recommended active therapy to help these patients, there has been great optimism in some quarters, while in others the old pessimism has prevailed. Today the view on the possibility of achieving results in individual cases has become more realistic.

The patients included in this study, to a great extent, received intense physical treatment by a specially trained staff. The observation time is still too short for numerical evaluation of the results. Nor will the many details of the treatment be discussed. Only a few general reflections will be made, as brief and preliminary conclusions from the experience gained.

One conclusion seems definite.

Most patients will improve on intense physical treatment. In those most mentally retarded, the only achievement possible will be to prevent the patient from stiffening into distorted positions. It may be questioned whether the results are worthy of the effort.

Severe motor symptoms are improvable only to some extent. However, in a relatively intelligent child any improved ability is important. In patients who arrive early for treatment, preferably in the first year of life, and who have moderate motor disorders, the results have been encouraging.

These patients must be systematically trained in all motor qualities which in a normal child come naturally.

Rehabilitation of severe cases which arrive late for treatment is more difficult. The reason possibly is partly that the physiological time for acquiring the ability concerned has passed, partly that the child may have adopted wrong movement patterns that must be removed before more adequate ones can be taught. This problem particularly applies to the athetoids with marked tension. These are the most handicapped in spite of an often normal intelligence. The treatment of previously neglected athetosis tends to be the most difficult.

Teaching the neglected spastics to walk may also be difficult or impossible. But the great majority of these patients will to some extent be able to use their hands. Nor are their speech disorders usually as pronounced as in the severe athetoid cases.

The training of ataxic patients is as a rule more rewarding. They have a natural tendency to spontaneous improvement during the years of childhood, as they gradually learn to depend on vision for orientation in space.

Even if all cerebral palsy patients could have optimal treatment,—a prospect which in Norway is as yet far off—more than partial rehabilitation of the severe and moderate cases would hardly be possible.

But untreated, their situation is hopeless. They will be reduced to a completely helpless, vegetating, and resigned existence in institutions for cripples, or mental defectives, or in their homes, imposing a severe strain on those nursing them.

All considered, one is justified in stating that: The great majority of cerebral palsy patients may derive benefit from some form of treatment, so that their lives may be happier than if left to themselves. In the most severe mentally defective, only modest improvement can be expected. On the other hand, in the mild cases with normal intelligence, intense therapeutic treatment may reduce their disabilities to such extent that it will not noticeably disturb their future lives. The larger middle group with severe or moderate motor disorders will with the present therapy, in spite of some improvement, enter upon adult life more or less handicapped.

The fact that the treatment used today is purely empirical should be kept in mind. Parallel with the increasing neuro-anatomical knowledge, the future surely will bring new and better physio-therapeutic treatment methods based on sound patho-physiological principles of internal, orthopedic, or neuro-surgical nature.

To work out adequate methods for prophylaxis must be the central task in the combat of cerebral palsy. The only possible way is through scientific investigation of the etiology of the disease.

Accepting the theory that the disease essentially is due to neonatal cerebral injury, the main task will be continued study of the anatomy, physiology, and pathologic anatomy of the brain in the newborn, and to find effective methods for prevention of cerebral injuries in connection with birth.

SUMMARY

Page 1–4.

The introduction gives a brief historical survey of cerebral palsy and an account of the various investigations of the frequency of the disease.

Page 5–6.

The material is based on anamnestic information and on clinical examinations of 370 children suffering from cerebral palsy.

Page 7–10.

To illustrate the etiology of the disease, data are presented. The material shows a male predominance, 60 % against 40 % of females.

A predominance of first-born children is statistically significant (52.7 %).

Page 11.

Possible genetic causal factors: Among the 370 patients familial occurrence on possible genetic basis was reported in siblings of two families. In two cases, cerebral malformations were demonstrated.

Page 12.

Other prenatal factors: There was no increase of maternal morbidity, nor was there information of possible external factors that might have caused injury to the fetus during the pregnancy. Malformations known to be thus caused were not demonstrated in any case.

Page 13–22.

Natal factors: Information regarding the course of birth showed pathologic birth in 43.8 %, protracted birth and breech presentation being the most common forms.

In 47 % of the children, information suggested perinatal asphyxia and/or symptoms of cerebral injury.

In 26 children (7 %) the information pointed to kernicterus in the neonatal period.

28.2 % of the patients were prematures (birth weight under 2500 gms). As many as 49 % of the patients with bilateral spasticity were prematures, and of these a relatively large percentage had very low birth weight. Pathologic birth was less frequent among the prematures than in the total number of cases (25 %).

On the other hand, the material also shows a statistically significant increase in the number of large babies with birth weight over 4 000 gms.

The percentage of normal birth weights (2500–4000 gms) thus is considerably lower than in a normal population (55 % as against normally 80–85 %).

The material includes 25 pairs of twins. In 15 cases, the other twin was healthy, in 6 cases it was stillborn. In two pairs of twins both children had cerebral palsy.

Page 23.

Postnatal factors: In 18 cases (5 %) there was information of postnatal cerebral infection or other cerebral injury that might be the presumed cause of their cerebral palsy.

Page 24–36.

The etiological conclusions to be drawn from these data are discussed.

They do not indicate an essential etiological importance of hereditary genetic factors or external fetal injuries in the organogenetic period to the development of cerebral palsy. But several conditions point to a dominant etiological importance of perinatal brain injuries.

In a comparatively small group these cerebral injuries are due to kernicterus. It is pointed out that kernicterus is not rare in prematures without blood-group incompatibility, and the possibility is suggested that mild cases of kernicterus may occur, undiagnosed in the neonatal period, leading to cerebral palsy.

Reference is made to animal experiments, autopsy findings, and clinical observations that point to deep-seated anoxemic cell lesions and hemorrhages in connection with birth as the main cause of cerebral palsy. The frequent occurrence of prematurity and clinical symptoms of asphyxia/cerebral hemorrhage in this study supports the view, but cannot be considered definite evidence.

More significant is the great number of pathologic deliveries and the demonstrated predominance of children with birth weight over 4000 gms.

It must be presumed that the same cerebral injuries which cause perinatal mortality, when of sublethal degree are also responsible for cerebral palsy. The prophylaxis of cerebral palsy must be aimed at preventing these injuries.

In about 5 % of the patients the disease probably was due to infective, anoxemic, or vascular injuries during infancy after the neonatal period.

Page 37–40.

Some remarks on the diagnosis of cerebral palsy.

Page 41–47.

The classification of the clinical types of cerebral palsy is described. The type division in the present study is the following.

Uncomplicated spasticity (56.7 %) with the subgroups of spastic hemiparesis (24 %) and spastic diplegia (32.6 %). Uncomplicated athetosis (14.3 %). Uncomplicated ataxia (6.5 %). The remaining 22.4 % of the patients, not referable to any of these types, but presenting a predominant mixture of pyramidal and extra-pyramidal symptoms, were collected into a special group.

Page 48–60.

Pneumoencephalography was made of 105 of the 370 patients. In 79 the examination permitted an evaluation of the ventricular system. 16 % were found to be normal. 84 % showed pathologic dilatation of the ventricular system. Two types of pathologic findings were distinguished: those observed in spastic hemiparesis and those seen in all other types of cerebral palsy. In hemiparesis a pathologic finding was frequent (in 15 out of 16 cases). One patient showed normal ventricular system and atrophic changes of the cerebral surface. In the remaining 14 there was dilatation of the ventricular system. Asymmetry of the ventricular system was a regular finding. In 11 cases the changes were bilateral, always with dilatation most marked contralateral to the hemiparesis. In three there was dilatation of the lateral ventricle only on the affected side. Nine of the 14 patients had dilatation also of the third and fourth ventricle.

Among all the other types of cerebral palsy, PEG was pathological in 51 of 63 patients. Regardless of the clinical type, the pathologic findings were strikingly uniform, with mainly symmetrical dilatation of the lateral ventricles, and often dilatation also of the third (41 patients) and fourth ventricle (11 patients). The conditions of the sulci on the cerebral surface were estimable in 44 of the examined cases.

The shape of the sulci was pathological in 35.

The pneumoencephalographic findings seem to suggest that in cerebral palsy there is, besides other processes, possibly a deep-seated central patho-

logic process, probably connected with perinatal injury, which is presumed the most important cause of the disease.

There is reason to believe that correlation exists between the degree of pneumoencephalographic changes and the degree of motor and mental defects in the patient. The pneumoencephalographic picture in cerebral palsy is strikingly like that seen in epilepsy without neurological symptoms.

Page 61–65.

It is suggested that organic epilepsy, cerebral palsy, and mental impairment due to cerebral lesions should be considered a pathologic entity, with the same etiology and the same pathologic-anatomical basis.

Intelligence tests were attempted on 212 patients and the intelligence was found normal in 43.9 %, I.Q. between 85 and 50 in 21.7 %, and under 50 in 34.4 %. I.Q. was found the most reduced in the mixed group, the least in athetosis.

Page 66–84.

Electroencepahlographic examination was made in 223 of the 370 patients. Eighty-eight (39.4 %) gave no pathologic finding. Thirty-seven (about 17 %) showed slight general dysrhythmia. In the remaining 98 patients (about 44 %) EEG was distinctly pathological.

In the mixed group, clinically the most severe one, EEG was found normal in no less than half the number of those examined. Apart from these cases there was, on the whole, good correlation between the clinical findings and EEG. Thus, in hemiparesis, dysrhythmia usually was found contralateral to the paresis. 82 of the 370 patients (22 %) had a history of convulsions. Within the clinical types, convulsions were the most frequent in spastic hemiparesis (34.8 %), the least in ataxia and athetosis (12.5 % and 7.5 % respectively). Sixty-one of the 82 patients had EEG examination. Six showed normal EEG, and in nine it was pathological without epileptogenic foci; 46 had one or more epileptogenic foci.

Epileptogenic foci (spike foci) also were found in 27 patients without manifest convulsive seizures. The location of the epileptogenic foci in the 73 patients were scattered over the whole of the brain, with slight predominance in central and temporal regions. A location in the posterior part of the brain, was predominant in the younger patients. Prematurity, pathologic birth, and symptoms of asphyxia/cerebral hemorrhage in the neonatal period occurred as often in those with convulsions as in the total number of cases. But among patients with epilepsy without cerebral palsy, these conditions were considerably less frequent than in those with cerebral palsy. On the other hand,

in epilepsy alone, history of familial occurrence of convulsions is far more frequent than in the convulsion group of cerebral palsy.

The I.Q. level, on an average, was considerably lower in the cerebral palsy patients with convulsions than in the cases in general.

On the whole, epilepsy in cerebral palsy responds as favourably to anti-epileptic medicational therapy as do simple epilepsies.

In only four patients did the initation of physical treatment appear to induce epileptic seizures.

Page 85–88.

Strabismus was demonstrated in 53 patients, and centrally conditioned reduction of vision in seven.

Definite reduction of hearing was found in 19 patients, mostly in athetoids, in the form of high tone loss. Dysarthria occurred in 80 of 253 patients (31.5 %). It was the least frequent in patients with spastic hemiparesis, the most frequent in the athetoids.

Page 89–98.

The study includes six autopsies.

Page 99–101.

It is pointed out that although much may be achieved by physical treatment of cerebral palsy patients, the main task in combating the disease lies in prophylaxis.

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THE CHILDREN'S CLINIC OF THE UNIVERSITY OF TURKU.
HEAD: PROF. T. SALMI, M.D.

CAPILLARY ERECTION AND LUNG EXPANSION

AN EXPERIMENTAL STUDY OF THE EFFECT OF LIQUID PRESSURE APPLIED TO THE CAPILLARY NETWORK OF EXCISED FETAL LUNGS.

by

S. JÄYKKÄ

TURKU . UUDEN AURAN OSAKEYHTIÖN KIRJAPAINO . 1956

To my Wife and Children

PREFACE

The basic idea which is presented in this paper to explain the aeration of the lungs of a newborn infant was first reported at a staff meeting of the Children's Clinic of the University of Turku in the autumn of 1953. From this date, Prof. Toivo Salmi, M.D., the Head of the Children's Clinic, has in many ways encouraged me and facilitated the progress of my studies. For this I wish to extend Prof. Salmi my best thanks.

I have later lectured on my work to larger audiences, first at the Eleventh Northern Pediatric Congress in Oslo in 1954, and published a preliminary report on the subject entitled: A New Theory Concerning the Mechanism of Initiation of Respiration in the Newborn (Acta Pediatrica, 43: 399, Sept. 1954.)

The human lung material used in the model experiments has been obtained from stillborn infants delivered at the Lying-in Hospital of the City of Turku. The lung specimens were prepared at the Department of Pathological Anatomy of the University of Turku. To Prof. Osmo Järvi, M.D., the Head of this Department, I wish to acknowledge my gratitude for this continued interest and cooperation.

After having made some progress in my work, I was fortunate in being able to obtain invaluable advice from Prof. C. Wegelius, M.D., and Docent J. Lind, M.D., experts in fetal hemodynamics. Through the courtesy of Prof. Wegelius, I had the opportunity of showing some preparations and of discussing my results with Prof. B. Patten, M.D. I am greatly indebted to these persons for their favorable criticism and encouragement.

The schematic drawings of this publication have been made by my sister, Mrs. Helvi Helanko, Ph. M. To her and to Miss Heli Riikilä, registered nurse, and Mrs. Aili Ryynänen, Ph. M., librarian, I am very grateful for their assistance. For the translation of this publication, I wish to thank Mr. E. R. Korte, Ph. M.

Financial support for this investigation has been received from the Emil Aaltonen Foundation and in the form of a Government Research Grant awarded by the University of Turku.

Turku, April, 1956.

Siinto Jäykkä.

TABLE OF CONTENTS

I. INTRODUCTION

When birth takes place and the placental circulation is interrupted, the lungs and the cardiopulmonary blood circulation enter a new phase which is necessary for the continuation of life in the newborn child. Although the studies made up to 1900 had not led to results which would have permitted reliable conclusions about the changes that occur in the fetal blood circulation and their reasons, it appears that GERARD (1900) and WELLS (1908) already surmised that rapid changes must take place in the the circulation. They both concluded that it is necessary to differentiate between the occlusion of the ductus arteriosus and its later obliteration. The same view appears to be the main theme of Potter's writings. In 1954 she wrote that "the histologic differentation and the functional potentialities at the time the fetus is converted from a parasite to an independent individual, and the manner in which they respond to the change from an aquatic to a terrestrial environment must be understood if the difference between normal and abnormal process is to be properly evaluated".

The closer study of the rapid changes in the blood circulation at birth became possible only after the development of suitable X-ray and cinematographic apparatus. Cineangiographic studies have been published during the 1940's.

The changes in the blood circulation and the lung expansion that take place following birth seem to have been studied in most cases as two unrelated phenomena; very little attention has apparently been paid to their possible interdependence. It is natural to assume that after lung expansion has occurred and oxygenation has become the function of the lungs, the blood flow through the pulmonary circulation must increase. This leads one to enquire whether the increased circulation through the lungs can also participate in effecting the expansion of the lungs. When the structure of the fetal

lung is recalled, one may apply to it the following mechanical parallel: a folded elastic tube tends to straighten out when the pressure within it increases. All the necessary conditions for such an occurrence seem to be fulfilled at the time of birth. The capillary network of a lung in the atelectatic state represents a system of extensively folded crumpled elastic tubes in which the blood flow can increase immediately after birth. These purely theoretical considerations gave cause to undertake an experimental study of the process of lung expansion in excised lungs.

II. THE FETAL CARDIOPULMONARY CIRCULATION

In the following we shall review the blood circulation in the fetus and the newborn with greater emphasis on the functional than on the anatomical aspects since the latter are well known and are of lesser interest. On the other hand, the difference between the fetal and adult circulations and the ability of the circulation to change rapidly from the former to the latter type at birth are worth closer examination.

1. *The branching of the blood flow in the right atrium. The development of the via dextra and via sinistra.*

The special structure of the fetal heart was already noted by GALEN. A detailed histological review on this subject has been written by BARCLAY, FRANKLIN and PRICHARD in The Foetal Circulation.

On the basis of the anatomical structure, WOLFF (1776) and SABATIER (1778) presented a hypothesis to explain the flow of blood through the right atrium. The special anatomy of the right atrium of the fetal heart is seen in Plate 1.

It seems that the inferior and superior venae cavae are inclined relative to each other so that the blood streams flowing through them do not intermingle. The blood streams appear to be further kept apart by the Eustachian valve, which forms a continuation of the inferior vena cava wall projecting into the right atrium. On the basis of this anatomical feature, the Wolff-Sabatier hypothesis assumes that the oxygenated blood from the inferior vena cava does not mix with the venous blood coming from the superior vena cava. This separation of the two blood streams promotes the development of the fetus by directing the oxygenated blood to the more important organs, the heart and upper part of the body, while the venous blood

is diverted through the ductus arteriosus to the placenta for reoxygenation.

The blood route from right to the left through the foramen ovale is referred to as the via sinistra, while the route through the right heart to the ductus arteriosus is known as the via dextra (BARCLAY *et alii*).

Although the anatomical features evidently support the Wolff-Sabatier hypothesis, various experiments performed on living fetuses yielded results that did not conform with the hypothesis (POHLMAN 1907, KELLOGG 1928). It was established that the blood streams mix completely in the right atrium. KELLOGG's results were not however fully concordant since he found that in some experiments the two streams seemed to be partly separated. This finding he ascribed to experimental factors. PATTEN, SOMMERFELD and PAFF (1929) took measurements of the inlets and outlets of the fetal heart and came to the conclusion that the mixing of the blood streams is unavoidable, especially when it is taken into account that the valve of the foramen ovale tends to obstruct the flow of blood through the opening.

The WOLFF—SABATIER hypothesis received new support from the measurements of the fetal blood gas tensions made by HUGGETH (1927) and especially from the similar measurements of BARCROFT. These authors found that the oxygen saturation was greater in the samples taken from the via sinistra than in those from the via dextra. They concluded that the mixing of blood in the right atrium is not complete.

Studies similar in principle to those of POHLMAN and KELLOGG were undertaken by WINDLE and BECKER (1940). Whereas the former authors injected starch granules, the latter authors injected india ink into the fetal blood circulation. The experiments also differed in that WINDLE and BECKER left the placental circulation intact, while the former authors removed the uterus along with the fetus and thus interrupted the maternal connection. This fact may have had an important influence on the results of the experiments. WINDLE remarks in particular that the results depended on whether the experimental animals were in good condition or not. When the experimental animals were vigorous, all, or almost all, of the blood that

entered the heart from the inferior vena cava flowed through the left heart, but when the animals were "in a dying state the slaggish stream of blood did mix in the right atrium". It may be mentioned in this connection that also BARCROFT and BARCLAY later expressed the same opinion, namely, that the experimental animals must be in very good condition.

Undoubtedly the best method of investigation is to use cineradiography. Such studies have been made by BARCLAY and his coworkers (1941) on lamb and by LIND and WEGELIUS on human fetuses (1949 and 1954). According to these authors, the blood is distributed in the right atrium as follows: when radio-opaque is injected into the internal jugular vein, the major part of the contrast medium goes through the via dextra, and only a small part passes through the foramen ovale into the via sinistra, but if the contrast material is introduced into the umbilical vein the greater part goes through the via sinistra and lesser part through the via dextra.

A recent study has led back to the opinion of POHLMAN and KELLOGG. According to BOHRN, DAWES, MOTT and WIDDICOMBE (1954), blood mixes in the proportion of about 2 : 1 in favour of the inferior caval stream in the right atrium, and in the left heart, blood from the pulmonary veins is added. "The ultimate result is that the oxygen content of blood in the brachiocephalic artery is greater than that in the umbilical artery as HUGGETH (1927) showed, but that the net gain to the fetus (as compared with the oxygen content if mixing had been complete) is very small."

2. *Via dextra and ductus arteriosus.*

When we follow the distribution of blood when it comes from the right ventricle to the pulmonary trunk we begin to enquire to what extent it flows through the lungs and through the ductus arteriosus. The anatomical features give some clue to the situation.

It is known that the muscle of the right ventricle is at least as thick as or even thicker than the muscle of the left heart in the fetus (PATTEN). The large calibre of the ductus arteriosus was pointed out

by NOBACK and REHMAN (1941). In thickness it is equal to or greater than the aortic arch, the pulmonary artery or the descending aorta.

Some work has been done to evaluate the blood flow through the lesser circulation during the fetal period, but discrepant results have been obtained.

On the basis of anatomical measurements conducted post mortem, PATTEN (1930) expressed the opinion that the pulmonary circulation prevailing during the fetal life is sufficient to effect adequate oxygenation even after respiration has begun.

ABEL and WINDLE (1939) determined the iron contents of ashed lungs of guinea-pig fetuses, part of which had been permitted to breathe freely and the rest had been prevented from breathing by clamping the tranchea. Since the iron contents were the same in both groups the authors concluded that a pulmonary circulation is "already present in the lungs during late prenatal life which is wholly capable of caring for oxygenation pending the assumption of respiration."

The blood content of the lung is influenced also by the flow from the bronchial arteries. It seems that very little is known about the quantity of this flow during fetal life.

Direct observations of the extent of the fetal pulmonary circulation are few. The results of BARCLAY and his coworkers show that the pulmonary arteries become filled with contrast medium also when the fetal circulatory pattern prevails.

Observations on human fetuses (LIND and WEGELIUS) have revealed that "the fetal pulmonary circulatory system shows only slight filling with the opaque contrast medium, an expression of its assumed partial segregation from the general circulation during fetal life."

When, further, the preponderance of the right ventricle and the large calibre of the ductus arteriosus are noted, the question of their physiological purpose during fetal life arises.

In addition to the hypothesis of SABATIER that the purpose of the ductus is to lead the venous blood past the lungs to the placenta for reoxygenation, only one other possibility has been suggested by PATTEN. He writes that "the ductus arteriosus thus serves during fetal life as a means of balancing right and left cardiac output and, in so doing, acts as what might be called the exercising channel of the right ventricle."

III. THE NEONATAL CARDIOPULMONARY CIRCULATORY SYSTEM AND THE CHANGES OCCURRING IN IT

After birth the physiological state of the fetus undergoes a radical change. The lungs begin to function suddenly and the cardio-pulmonary circulation is altered by the closure of the via dextra and via sinistra. The closure of these fetal channels involves a functional occlusion which is subsequently rendered permanent by anatomical obliteration.

1. *The closure of the via dextra.*

The opinions on the functional closure of the via dextra have passed through a long phase of development.

The older views of the closure of the ductus arteriosus have been reviewed by, among others, WELLS (1908) and SWENSSON (1932), who have summarized the proposed mechanical agents of closure as follows: the expansion of the bronchi; thrombosis in the lumen of the ductus; bending of the aorta; respiration and the rearrangements of the organs of the thorax; a valve closes at the junction of the ductus and aorta.

The opinion evolved that the histological structure of the ductus arteriosus is responsible for the functional closure. The histological differentation of the ductus is credited to LANGER (1857). According to HAYEK (1935) the muscle fibres in the walls of the ductus are geometrically arranged so that they can effect closure of the ductus by undergoing contraction. Detailed histological studies of the structure of the wall of the ductus have been made by SWENSSON (1939) and JAGER and WOLLENMAN (1942). They concluded that both the intima and media consist of circular muscle fibres, the media also containing longitudinal fibers. The structure of the ductus

arteriosus has given reason to call it the muscular artery to differentiate it from other elastic arteries.

Other indirect evidence for the way in which the ductus closes has been presented by HAMILTON, WOODBURY and WOODS (1937). As long as the ductus remains patent, the blood pressure is equal in the right and left ventricles. The development of a pressure difference after birth suggests an early closure of the ductus.

Direct observations were, however, required before reliable conclusions could be drawn about the closure of the ductus. Animal experiments have been conducted by BARCROFT, BARCLAY and their coworkers with this object in mind from the year 1938. LIND and WEGELIUS have performed similar experiments on human material (1954). The results of these authors make it fairly certain that the fetal circulation undergoes a radical change after birth.

There still remains, however; some doubt as regards the time these processes require to go to completion. BARCLAY *et alii* have observed that closure occurs in a matter of minutes after the cord is ligated. EWERET and JOHNSON (1951) injected radioactive phosphorus into the right ventricle and withdrew blood samples from the left pulmonary artery and the aorta. They concluded that "the ductus arteriosus remains functional for a considerable period following birth, but more marked reduction occurs at about nine hours post partum." The latest results of animal experiments (DAWES *et al.* 1953 b, BORN, DAWES *et al.* 1954) appear to indicate that a transition phase intervenes between the cessation of the fetal circulation and the initiation of the adult circulation. The closure of the ductus takes place gradually, but nevertheless the flow in the pulmonary circulation increases from three- to tenfold at birth. The increased pulmonary blood flow is caused by a reversal of the flow through the open ductus arteriosus. The initial vascular resistance is high and falls when artificial respiration begins.

According to BARCLAY *et alii* (1942) the closure of the ductus arteriosus reduces the pulmonary circulation time from 2.7 seconds to 1.5 seconds.

When the ability of the ductus arteriosus to undergo contraction has been established, the question arises as to what stimulus causes the closing apparatus to function.

The nerve supply of the ductus arteriosus is derived from the left vagus (BOYD 1941). Motor fibers are also found, but their origin still remains uncertain (BOYD 1941).

The effect of vagal stimulation on the closure of the ductus was first studied by BARCROFT, KENNEDY and MASON (1938). They observed that stimulation of the left vagus effected contraction of the ductus muscle, while the effect of stimulation of the right vagus remained inconclusive. KENNEDY and CLARK (1941, 1942) made a thorough study of the nerve pathways. They came to the somewhat surprising conclusion that nerve pathways are not necessary for the closure of the ductus. The ductus reacts by undergoing closure to the following stimuli: mechanical or electrical stimuli, injected adrenaline, injected oxygen, hemorrhage, natural and artificial respiration, and a number of miscellaneous stimuli. The ductus remains closed as long as the stimulus is maintained and opens when the stimulus ends. They considered the reaction of the ductus to be similar to that of any other hollow smooth muscle. They held respiration to be the most important stimulus, but the gas inhaled had to contain oxygen. Respiration of pure nitrogen did not effect closure of the ductus.

Owing to the uncertainty of the results of the studies relating to the closure of the ductus arteriosus, many questions are still left unanswered. Thus BARCLAY and coworkers have established by animal experiments that a closed ductus may reopen again. This is followed by a deterioration of the condition of the animal under experiment. Observations similar to these were made by LIND and WEGELIUS in human fetuses. They found that in cases of asphyxia the fetal channels were open. The question arises which is the primary, which the secondary occurrence. Does the asphyxia cause the circulation to revert to the fetal type or does the reversion lead to asphyxia?

DAWES *et alii* have observed in the fetal lamb that the ductus is able to close temporarily but nevertheless remains open for several hours following birth. The pathological condition that results when anatomical obliteration of the ductus does not occur is well known. What then is the normal reaction of the ductus at birth when the process has not been disturbed by manipulations such as opening of the thorax, pressure measurements and injection of contrast medium?

Kennedy and Clark are the only authors who have clearly expressed their opinion of the normal reaction of the ductus. They write: "This active muscular contraction with obliteration of the lumen is the first phase of closure of the ductus arteriosus and occurs during the first few minutes following birth, under normal circumstances, beginning with the establishment of effective respiration. In normal animals the ductus remains closed after this initial closure and is finally transformed into the ligamentum arteriosum."

The anatomical closure of the ductus arteriosus takes place two months after birth according to Scammon and Norris (1918) and after 6—8 weeks according to Patten (1947), but according to Ewerert and Johnsson (1951) it is completely closed on the 15th to 18th day post partum. In this connection we may note the decided opinion of Kennedy that the examination of the closure or non-closure of the ductus with a probe post mortem is an entirely worthless procedure.

2. *The closure of the via sinistra.*

The modern view of the cessation of the function of the foramen ovale has been accepted for a long time and apparently no other opinion has been ever presented. In conformance with Patten (1947) this process may be described in following manner. The valvula foraminis ovalis is a one-way valve which is thrust aside by the blood stream. After the blood flow through the lungs increases after birth, the pressures in the two atria first equalize and then the pressure in the left atrium begins to overweigh that in the right atrium and closes the valve. A similar description of the process has been given by Potter (1952) and also by Dawes (1953 a).

The anatomical obliteration of the foramen ovale is a slow process that occurs late and is characterized by considerable individual variation, but does not go to completion earlier than the last third of the first year after birth (Patten 1947).

IV. THE FETAL LUNG AND THE CHANGES THAT IT UNDERGOES AT BIRTH

The opinions on the structure of the fetal lung and its development are so varied and discordant that one of the most distinguished authorities, E. POTTER (1953), has written that "one feels that the lung must have a different structure and function in different parts of the country or the world." POTTER also mentions that animal material has been extensively used in the investigations and the results have been extended to apply to man without reservation. A normal fetal or neonatal human lung is only rarely available for examination, since the fetus and the newborn infant succumb to pathological processes. In addition artificial respiration and other resuscitation procedures may alter the condition of the lungs.

GRUENWALD (1947) has remarked that the unaerated lung of a stillborn infant, as seen upon gross examination, has been considered to represent the fetal pattern. He proposes that in evaluating the size of the lung one must distinguish between aeration, expansion by liquid, and atelectasis.

It is thus difficult to obtain on the basis of the published reports an opinion of the architecture of the lung during fetal life and of the changes that take place in the lungs when the fetus enters the neonatal phase. Contrary and more or less divergent opinions have been expressed about the following aspects:

1. Primary and secondary atelectasis.
2. Lung expansion and aeration.
3. The occurrence of fetal respiration and its influence on the structure of the lung.
4. The behavior of the capillaries during the expansion.

1. *Primary atelectasis.*

The study of the fetal lung originates mainly in the work of Jörg (1835), for he was the first to recognize that atelectasis is a physiological state peculiar to the fetal lung. Jörg also coined the term atelectasis which he defined not on the basis of appearance but on the basis of the function of the lung: "In unvollkommener Ausdehnung oder Erweiterung der Lungen durch Luft." In point of fact, observations had been previously made on the fetal lung, but the absence of air and the solid consistency was attributed to congenital pneumonia (Billard 1832).

Primary atelectasis has up to recent times been defined in accordance with Jörg (Ahvenainen 1948). Very little information about the actual structure, especially the forms of the lumens, can be found in the literature.

The interest of the older investigators centered mainly on the cells lining the alveoli in the fetal and neonatal lung (Croix 1883, Flint 1906, Stewart 1923, Seeman 1931, Bensley and Bensley 1935, Bensley and Gross 1935). The epithelial cells were considered to be cuboidal before aeration and were assumed to become flattened through stretching. Furthermore, according to Stewart, the cytoplasma undergoes a "sort of fatty metamorphosis" which is accompanied by overlapping of the epithelial cells. The changes seen by Stewart assist the epthelium in adapting itself to the stretching resulting from the aeration. Clements later (1938) called attention to the overlapping described by Stewart but was unable to confirm its occurrence by means of his own observations. Potter has not observed any difference between the epithelial cells in a mature fetus and in an infant who has lived several days.

The opinions of the nature of primary atelectasis differ radically from each other in that some authors (Snyder and Rosenfeld 1938, Ahvenainen 1948) have considered primary atelectasis to involve also the state known as expansion with liquid. According to these authors no change takes place in the condition of the lumens when aeration occurs. Snyder and Rosenfeld have been decided in their opinion and have proposed that the air spaces are not in state of collapse during the intrauterine stage, but are fully developed and

filled with amniotic fluid. Of particular interest in this connection is the observation of AHVENAINEN that the lumens expand during fetal aspiration of amniotic fluid if the placental circulation is disturbed or interrupted, since there were among SNYDER's and ROSENFELD's cases a number with compressed cords. HAM and BALDWIN (1841) have presented a middle course; according to these authors opening-up is in operation before birth and breathing of air merely accentuates it.

An opinion of the nature of primary atelectasis began to form gradually when various conditions differing from each other in structure were distinguished: initial atelectasis, partial expansion with amniotic fluid, and partial expansion with air (WHITEHEAD, WINDLE and BECKER 1942). The latter authors published typical photomicrographs of each condition.

After injecting dyed gelatine into the air spaces, HAM and BALDWIN (1941) saw that the spaces have a pronged or prickly outline. The best description, which may be considered to correspond to the present views, is the comparison of the primary atelectatic lung with a crumpled sack, as proposed by POTTER (1950).

The existence of amniotic fluid in the future air spaces during fetal life is generally accepted (ADDISON and HOW, SNYDER and ROSENFELD, AHVENAINEN, POTTER). As soon as aeration occurs, the amniotic fluid is rapidly absorbed by the rich capillary bed, as shown by the animal experiments of POTTER. POTTER has also presented the view that the entrance of amniotic fluid into the air spaces is necessary for the intrauterine development of the lungs. This conclusion she drew from observations of cases in which amniotic fluid was absent and inhibition of lung growth had occurred.

The divergent view of WHITEHEAD *et alii* (1942) may also be noted. Their opinion is that the liquid present in the lungs is not amniotic fluid, but transudate, which flows from the lungs to the amnion.

2. *Secondary atelectasis.*

LICHTHEIM (1879) observed that in animals air may be resorbed from the lungs if the bronchus is occluded; a condition results which

is known as secondary atelectasis. UNGAR (1909) and YLPPÖ (1919) assumed that the atelectasis seen in neonatal autopsies is produced in the manner proposed by LICHTHEIM. Weak blood circulation, mucus in the respiratory passages and edema were considered to promote the development of secondary atelectasis, especially in premature infants. Their views did not, however, gain acceptance. Older investigators (DOHRN 1891, ECKERLEIN 1891, PEISER 1908) had stated that primary atelectasis disappears gradually and the atelectasis observed in newborn infants is a residuum of the fetal lung that has not undergone aeration. Also later investigations have confirmed the view that primary atelectasis disappears gradually (ADDISON and HOW 1913, AHVENAINEN 1948, WHITEHEAD *et alii* 1942).

Various opinions exist as to the possibility of differentiating between primary and secondary atelectasis. FARBER and WILSON (1933) postulated that secondary lung collapse can be distinguished from primary atelectasis by the fact that cuboidal epithelial cells cover the alveoli that have not been stretched previously, whereas flattened cells cover those that have been subjected to stretching. This view has been opposed by POTTER (1953) who considers that FARBER's and WILSON's material has been inadequate and abnormal.

AHVENAINEN (1948) studied in detail the difference between primary and secondary atelectasis by examining the following features: the size of the lumens, the thickness, course and shape of the walls, capillaries, endothelial cells, alveolar epithelial cells, mesenchymal cell nuclei, and general aspect of the lung. He was unable to detect any clear differences in these respects. He also later stressed (1953) the difficulty of distinguishing between primary and secondary atelectasis.

POTTER's views on this point are quite clear. She writes: "It is entirely possible, however, to differentiate histologically between lungs that have never contained air and those from which air has been resorbed after the alveoli have been expanded. In the former the entire pulmonary tree shows a uniform pattern of ductal and alveolar lumens. In the latter, the alveoli from which air has been resorbed are collapsed and the walls are juxtaposed."

3. *Lung expansion.*

The process of lung expansion has been studied in dead material by numerous investigators. FARBER and WILSON (1933) have reported that a pressure of a least 25 cm of water is required to effect the expansion. WILSON, TORREY and JOHNSON (1937) observed that even a pressure of 18 mm Hg was unable to expand the lung up to the alveoli. This latter pressure furthermore caused injury to the lungs. GRUENWALD (1947) found that a pressure of 10—21 cm of water was necessary when the lung was insufflated with air, but only a pressure of 5—10 cm of water when the lung was expanded with saline.

DAY *et alii* (1952) were the first to call attention to the time the pressure was required to act. They proposed the hypothesis "that injury to lung arises from distention, not from pressure, and that distention is proportional not only to pressure but also to the time during which the pressure is exerted". This impulse principle of DAY implies that the lung can be safely inflated with a pressure of 40 cm of water if the time of application is only 0.15 second. The prolongation of the time to 0.2 second may result in damage to the lung. Rat lungs rendered atelectatic with oxygen were employed in the experiments.

GODDARD and coworkers have repeated Day's experiments using an improved technique (1955). They found that pressures up to 20 cm of water do not effect expansion of the human lung, pressures from 20 to 60 cm of water produce uniform expansion, while pressures exceeding 60 cm of water result in overexpansion and rupture. The time the pressure was allowed to act was in all cases 0.2 second. These authors also recorded the duration of inspiration in newborn infants and found it to vary from 0.3 to 0.6 sec. in premature infants and from 0.5 to 0.6 sec. in full-term infants.

According to SMITH (1942), an infant is able to produce a pressure difference of 40 cm of water if he is allowed to breathe under a face mask connected to a manometer. DONALD found (1954) that the intrathoracal negative pressure may amount to 60 cm of water during the first inspiration.

4. *Aeration of the lungs.*

Several phenomena associated with the aeration of the lungs have not been satisfactorily explained and their investigation is still in progress. Of these may be mentioned the atmospheric pressure in the pleural cavity at birth and the later development of a negative pressure in this region.

BERNSTEIN (1882) observed that the lung of a newborn infant does not collapse when the thorax is opened. Atmospheric pressure thus prevails in the pleural cavity of the newborn infant. This was a marked difference from the situation in the adult. Since it was difficult to understand the presence of air in the lung of the newborn infant, BERNSTEIN proposed a quite unusual explanation for the phenomenon. He assumed that there is some kind of a hook system in the costovertebral joints which supports the thorax in the inspired position. This explanation, strange as it appears, is typical of the kind proposed to provide an explanation for the presence of air in the newborn lung.

HERMAN (1879) supposed that the lung tends to expand due to its own elasticity but that the expansion is opposed by the cohesive forces between the moist alveolar walls. Referring to this explanation, BERNSTEIN remarked that there is no cohesion within the fluid or in the lung since it is filled with amniotic fluid in the uterus.

OLSHAUSEN (1894) and LOESCHKE (1928) proposed explanations similar to that of HERMAN, but which differed in that the force that prevented the lung from expanding in utero was not a cohesive force but the intrauterine pressure. When the child is released from this pressure at birth, the lung expands and becomes filled with air.

The development of a negative pressure in the pleural cavity HERMAN explained by assuming that the thorax grows more rapidly than the lungs. This explanation can still be found in text books, e.g. TAYLOR, The Physiological Basis of Medical Practice, 1950: "The distention of the lungs increases, however, in later years since the thorax cage grows more rapidly than the lungs, the elastic pull in consequence also increases and with it the intrapleural negative pressure.

Several opinions have been expressed as regards the rapidity with

which the lungs become aerated. YLPPÖ concluded that complete aeration is effected during the course of several respirations, even in the case of premature infants. The present view as presented in most text books (SUNDAL) is that in accordance with the gradual disappearance of atelectasis, full aeration requires a period of several days. Both AHVENAINEN and POTTER, however, have stated that some observations seem to suggest that only a few respirations are required to effect aeration of the lungs.

A reliable description of the phenomenon was obtained when LIND and WEGELIUS succeeded in photographing the aeration process. In contrast to the earlier views, it was found that the lung of the infant becomes aerated with surprising rapidity. The photographic film does not show that the lungs are gradually filled with air by the respiratory movements; the process resembles the lighting up of a lamp. The air content does not seem to increase later when the lungs are examined repeatedly with x-rays. Parallel with the aeration, the shadow of the heart expands and then gradually returns to its previous size. Obviously it is not possible to conduct a histological investigation of the human lung at this stage, and hence the extent to which histological atelectasis invisible in the x-ray picture persists in the lung is not known. It seems that experiments to determine this have not been made even with animals.

5. *Intrauterine respiration.*

According to PREYER (1885), VESALIUS (1542) and WINSLOW (1787) already made observations on intrauterine respiration. A greater interest in the problem was awakened when AHLFELD (1888) published kymographic records which he claimed to relate to respiratory movements in the human fetus. Discordant views have also been presented and studies which both agree and disagree with AHLFELD's views have been published up to the present day.

The extensive publications on this subject which are based on experiments with both human and animal fetuses can be divided into two groups on the basis of the method of investigation.

1. Direct observation of the fetuses through the uterine wall or after their removal from the uterus.
2. Indirect observations after dye or thorotrast has been introduced into the amniotic fluid. The dye is aspirated by the fetus into the respiratory passages where it can be found after delivery.

It is generally admitted that the fetus can be induced to make respiratory movements by means of various stimuli (BARCROFT 1937 and BARRON 1937—38) but doubt has been expressed (PATTEN 1947) as to whether intrauterine respiration is a normal occurrence in undisturbed intrauterine existence. Authors who have unable to observe intrauterine respiratory movements are, e. g., ENGSTRÖM, RUNGE, SALMI and WINDLE, while authors who have are, e. g., PREYER, WISLOCKI, STEWART, BONAR and BLUMENFELD, SNYDER and ROSENFELD, REIFFERSCHEID and SCHMIEMAN, and DAVIS and POTTER.

If the fetus normally performs respiratory movements, one may ask whether the amniotic fluid is drawn in and forced out by the movements and to what depth, and whether aspirated amniotic fluid affects the structure of the lungs, i.e. whether it has an expanding effect. The views that have been expressed on these problems are varied.

AHLFELD and REIFFERSCHEID, K., (1911) considered that the respiratory movements are so feeble that the amniotic fluid cannot penetrate further than to the larynx or bifurcation. A similar view has been recently presented by MORISON (1952) who doubted whether the respiration can move the fluid enough to effect any exchange and thought that dyes and the like injected into the amniotic fluid can move as far as the terminal respiratory spaces by simple diffusion.

In a study of human fetuses of different ages, DAVIS and POTTER (1946) observed that a fetus weighing only 39 g in the 12th week of gestation aspirated thorotrast. They also remarked on the basis of their experiments that a fairly long time is required before thorotrast can become concentrated enough to produce a shadow. They mentioned this because WINDLE (1939) had been unable to find thorotrast in the lungs of guinea-pig fetuses with which he conducted similar experiments. In WINDLE's experiments, penetration of thorotrast up to the terminal divisions was effected only when the mother animal

was made to inhale air with decreased oxygen content or an increased carbon dioxide content. Both methods produced asphyxia in the fetus which in turn caused it to perform respiratory movements. WINDLE noted further that even in the asphyctic fetuses thorotrast did not in all cases penetrate further than the large bronchi.

The amniotic fluid is not considered to exert an expanding effect unless the fetus has been asphyctic and has strongly aspired the fluid (POTTER).

The aspiration of any substance, be it air or liquid, does not appear to be necessary for the occurrence of expansion, since many cases have been described in which no outside connection has ever existed owing to congenital larynx obstruction, but expansion has nevertheless taken place (FRANKENBERGER 1902, KOVÁCS 1933, POTTER and BOHLENDER 1941). KOVÁCS suspected that the expansion had been caused by the accumulation of mucus in the air spaces.

6. *The capillaries of the lungs and their behavior during the expansion.*

The ingrowth of the pulmonary capillaries and their density during fetal development have been described by numerous workers (MALI and RÄIHÄ 1936, KLEMOLA 1937). A further development is the progressive projection of the capillaries through the alveolar epithelium. According to PALMER (1936) this process begins during the sixth month and according to NORRIS *et alii* (1941) after gestation has lasted 5—6 months. POTTER has stated that the vascular development reaches a stage where the lungs are capable of performing oxygenation when the weight of the fetus has risen to 1000 g. This is probably one reason why a premature infant weighing less than 1000 g seldom survives.

It seems that very little attention has been paid by authors to the relationship between lung aeration and the reaction of the capillary network. The available information is to be found only in publications relating to other subjects. In the older literature there is a hypothesis propounded by HENSLEY (1872) according to which one cause of the

alteration of the air vesicles from an atelectatic state to a state of distension in the newborn infant is that blood propelled through the lung capillaries tends to straighten them out like the petals of an unopened flower-bud. The capillaries in the adult lung have also been considered by LIBERMAN (1872) and v. BASCH (1891) from the same aspect as HENSLEY. HENSLEY's hypothesis has not evidently been awarded any significance or it has been completely forgotten, since it is not mentioned in the newer literature. Contemporary writers such as PREYER (Specielle Physiologie des Embryo 1885) did not mention the hypothesis. Preyer does, however, present the following visionlike description of the relationship between the capillaries and the first act of respiration: "Die ersten Ausdehnungen der atelektatischen Lunge hat zur Folge ein reichlicheres Einströmen des Blutes der Pulmonal Arterien durch Aspiration. Die Lunge wird zugleich lufthaltig und blutreicher. Ihre Capillaren füllen sich mit grossen Geschwindigkeit." This description is in agreement with modern views. ADDISON and HOW, for instance, assume that the filling of the capillaries is caused by negative pressure that develops in the thorax.

MACKLIN and MACKLIN have dealt with the relationship between the capillary network and the the air spaces in the adult lung. Their views can, however, be also extended to the conditions prevailing in the infant at birth. They state that the physiological condition requires that expansion of the capillary network parallels the expansion of the air spaces, and vice versa. Imbalance may result, however, when "the alveolar zone becomes overdistended without there being a simultaneous equivalent swelling of the blood vessel." The imbalance may lead to lung rupture. The factor causing lung rupture they refer to as factor A. Imbalance, and hence rupture, may on the other hand occur if the capillaries contract without an equivalent narrowing of the alveolar envelope, factor B. In animal experiments they found that the insufflation of air into the lungs may cause distention of the tissues with the result that the lung resembles a spider's web when it is examined after microsection. The strands of the network are composed of mesenchyme and capillary vessels. They did not find it possible to effect entrance of liquid into the vessels of the distended lung even under a high pressure.

As an isolated observation, KRAFKA (1933) describes a very interesting experiment which has an important bearing on the present investigation. KRAFKA ligated the ductus arteriosus and then increased the pressure in the conus arteriosus to 60 mm Hg whereupon he observed that: "the lungs in the stillborn infant were made to "inflate" strikingly after the fashion shown when a tracheal cannula is inserted and artificial respiration is induced in the cat. Histologic sections of these lungs showed a marked distension of the walls of the alveoli." KRAFKA did not attempt to explain in any way the "inflation" that he found to result from the increased pulmonary pressure.

V. SUMMARY OF MODERN VIEWS ON THE PRENATAL AND POSTNATAL CARDIO-PULMONARY CIRCULATION AND RESPIRATION

1. *The prenatal pattern of cardiopulmonary circulation and respiration.*

Primary atelectasis prevails in the lungs.

The potential air spaces are filled with amniotic fluid.

The fetus probably makes feeble respiratory movements.

The ductus arteriosus and foramen ovale are patent.

The inferior caval blood stream flows for the most part through the via sinistra.

The superior caval blood stream flows mainly through the via dextra.

The flow through the pulmonary artery is very slight.

2. *The postnatal pattern of cardiopulmonary circulation and respiration.*

A radical functional change occurs in the pulmonary circulation at birth.

The blood flow in the lesser circulation increases as a result of reversal of the flow through the ductus arteriosus. The vascular resistance, initially high, and hence the pulmonary pressure, decreases with initiation of respiration.

The aeration of the lungs takes place instantaneously.

Atmospheric pressure prevails in the pleural cavity.

VI. THE PROBLEM

1. *Physiological aspects.*

In the mechanical respect the respiratory movements in a newborn child may be compared with the movements of a reciprocating piston. The maximum volume of air inhaled when the piston reaches the end of its stroke corresponds to the vital capacity. In full-term infants the vital capacity (inspiratory capacity + expiratory reserve volume) averages 25 cc. according to GODDARD *et alii* (1955). When the piston returns to its initial position, i.e. when relaxation of the diaphragm and thorax occurs, there still remains according to these authors 125 cc. of functional residual air (functional residual air capacity = residual volume + expiratory reserve volume) in the lungs. KARLBERG (1955) has found that the functional residual capacity is not as high as GODDARD has reported, being only 70 cc. in an infant weighing 2.5 kilograms. These figures show that more air has entered the lungs than corresponds to the maximum volume inhaled. It thus remains unexplained where the volume in excess of that of the inhaled air originates when aeration occurs. This total volume cannot develop gradually during the course of several respirations since in such a case a valve mechanism would be necessary in addition to the piston. The hypothesis proposed by OLSHAUSEN and LOESCHKE according to which the volume results from the release of the intrauterine pressure does not provide a satisfactory explanation of the observed phenomena. Their explanation would imply that the expansion of the thorax following the removal of the external pressure produces a negative pressure in the pleural cavity, but such a negative pressure has not been observed in the newborn infant. The film taken by LIND and WEGELIUS shows that aeration does not occur immediately after the child becomes exposed to the atmospheric pressure, but requires a certain period of time. These views are shown schematically in Plate 2.

2. *Clinical aspects.*

Positive-pressure inflation experiments have shown that a pressure corresponding to 20—40 cm of water is required to inflate the lungs through the bronchi. Hyperextension and injury of the lung occurs, however, if the pressure is applied longer than 0,2 second. GODDARD has found that the time of inspiration in a newborn infant is 0.3—0.6 second. It would thus seem that the the first inspiration must necessarily injure the lungs. Furthermore it is difficult to perform a lung inflation by means of rapid insufflation in the way in which it appears to take place according to the film of LIND and WEGELIUS. On the contrary, in inflation experiments the air is introduced gradually to different regions, and according to DAY's impulse principle, during safe inflation many impulses are required before the whole lung has expanded.

Cases have been reported in which cartilaginous obstruction of the trachea has occurred, but nevertheless microscope examination has revealed that lung expansion is complete. Expansion has also been found to occur in cases of diaphragmatic hernia, where the diaphragm movement has been insignificant (POTTER). It is therefore obvious that some other factor which promotes lung expansion must exist in addition to the respiratory movement.

By producing asphyxia in the fetus, it is possible to induce respiratory movements and cause the fetus to inspire amniotic fluid, whereupon lung expansion takes place simultaneously. On the other hand, a large number of authors believe that the fetus normally performs respiratory movements and inspires amniotic fluid, and added radio-opaque substances. Lung expansion does not, however, normally take place in utero although the fetus performs respiratory movements and inspires. It must therefore be assumed that there is some factor preventing lung expansion during the intrauterine phase.

VII. THE THEORETICAL BASIS OF THE EXPANDING EFFECT OF FLUID PRESSURE IN PULMONARY CAPILLARIES AND A WORKING HYPOTHESIS

We note, firstly, that the lungs receive blood by two routes, through the pulmonary and bronchial arteries, and secondly, that the air spaces can be divided into two parts, the conducting part and the respiratory part (MACKLIN). These two systems have their own capillary networks; those of conducting part are subdivisions of both the bronchial and pulmonary arteries, while those of the respiratory part are continuations of the pulmonary artery alone (Plate 3).

Before the respiratory apparatus begins to function, the air spaces are deflated and crumpled. The capillary network is extensively folded and the blood flow in the capillary network of the respiratory part slight. The following hypothetical picture of the sequence of events leading to respiratory function may be assumed.

The folds in the capillary network of the respiratory part straighten out and cause extension of the corrugated alveolar wall. The process may be termed *capillary erection.* This capillary erection effects an increase in the volume of the air spaces without the assistance of respiratory movements. The distended capillary network forms a supporting structure which prevents the alveoli from becoming atelectatic during expiration.

The cardiopulmonary blood circulation of the fetus thus provides a protective system. The respiratory apparatus will remain inactive as long as the pulmonary blood flow is slight and the main blood flow occurs through the via dextra. The activation of the respiratory region occurs with the beginning of flow through the lesser circulation and hence with initially high vascular resistance and high pressure. If the fetus performs respiratory movements in utero, the

amniotic fluid will only move back and forth in the conducting part, and all that is inspired will also be expired.

If capillary erection occurs while the fetus is still enclosed by amniotic fluid, respiratory movements will force amniotic fluid into the expanded respiratory part. The result will be what is termed ''expansion with liquid''. If the fetus has already been delivered, air will be drawn into the expanded area of the respiratory apparatus and ''expansion with air'' will result.

The above hypothesis implies that the aeration of infant's lung takes place by a process of erection which involves the capillary structure of the lung and is actuated by the change of circulatory flow at birth.

The experimental part that follows will be limited to a description of the apparatus of the lung that participates in the erection and to a presentation of qualitative results of model experiments performed with excised lungs.

VIII. MATERIAL

The material employed in the experiments comprised the lungs of stillborn human full-term and premature fetuses. The lungs and hearts were removed together in one mass. The lungs have been expanded by taking various possibilities into account. The various methods of effecting expansion are described in the next chapter, and the number of lungs used in each method is indicated. In addition to human lungs, the lungs of two lamb fetuses were employed in the experiments.

The lung capillaries were rendered visible by injecting macrodex containing india ink into the pulmonary artery.

During the first experiments it became evident that blood corpuscles in most cases obstructed the capillaries so effectively that the injected fluid was able to penetrate into only one of the lobes or into an even smaller region of the lung. For this reason the blood corpuscles were destroyed either by immersing the lungs in ether for several hours or by freezing them with solid carbon dioxide and then rapidly defrosting. Neither of the methods was ideal since amorphous substances still remained that tended to obstruct the capillaries. Furthermore, the ether had a tendency to fix the tissues. The best experimental material was obtained from fetuses that had been dead for such a length of time that hemolysis had occurred. Unfortunately, only a small number of these fetuses became available.

IX. THE EXPERIMENTAL METHOD

1. *The erectile apparatus of the lung.*

It is not possible to study the movement of the apparatus of the respiratory part of the lung by available methods. An attempt to film the postulated capillary erection by microangiography did not meet with success. It was therefore found necessary to study the process by fixing the preparations and searching for anatomically similar regions in each preparation which exhibited progressive variation from atelectasis to complete expansion. Lungs fixed with ether were found to be most suitable for this purpose. Before the sectioning, india ink was injected under a pressure of 80 mm Hg into the pulmonary artery.

2. *Expansion experiments.*

The expansion experiments were performed in three different ways depending on the process which it was the intention to imitate.

a) Insufflation with air under pressure through the bronchi; in this method the effect of respiratory movement unaided by capillary erection was imitated. This method is termed *inflation*. Lungs from six infants were experimented upon.
b) Expansion by means of liquid introduced into pulmonary artery. This method imitates the action of capillary erection unaided by respiratory movement. The method is termed *erectile expansion*. Lungs from 2 premature and 3 full-term fetuses were employed.
c) Combination of *inflation* and *erectile expansion*. Lungs from 3 premature and 4 full-term infants, and lungs from 2 lamb fetuses were used in the experiments.

Inflation was performed simply by forcing air through the bronchi under a pressure difference sufficient to effect entrance of air into the lung. As reported by previous investigators, the pressure had to be at least 20 cm of water. The two methods used, I and II (Plate 4), both produce a difference in pressure outside and inside the lung and they can be considered equivalent as long as the behavior of the capillaries is not taken into account.

The pictures taken in connection with the inflation experiments are presented together with pictures taken of clinical cases in which capillary erection has been weak or lacking. The clinical cases have been:

a) Premature infants, six in number.
b) Insufflated newborn infants, three in number.
c) One infant that died from profuse hemorrhage (melena).

The capillary erection forces may be weak in the lungs of premature babies for two reasons. First, as several investigators have found, the capillary network may be coarse. Second, the pumping force of the heart is weak and unable to effect a pressure in the pulmonary circulation.

Group b consisted of apneic newborn infants whose hearts functioned at birth. Evidently also the blood circulation had been in a state of collapse in these infants. If such an infant is subjected to artificial inflation or this is effected by resuscitation, a pure simple inflation is involved, the capillary erection being weak.

Cases of melena that have ended fatally are rarely encountered. Evidently lung expansion takes place in these in the normal manner, but subsequently a condition develops in which, as a result of profuse hemorrhage, the blood circulation collapses, but respiration continues. These cases thus involve the development of secondary atelectasis following the collapse of capillary erection in the respiratory part of the lung.

Erectile expansion has been effected in the experiments by injecting macrodex, with or without india ink, under a pressure of 80 mm Hg into the pulmonary artery of one lung. Compared with the normal pulmonary artery pressure, a pressure of 80 mm Hg may

seem high, but its use can be justified as follows. Dawes has established that the pulmonary pressure may rise to 80 mm Hg and more in the fetal lamb when the ductus arteriosus closes temporarily the first time. Model experiments have been conducted to reproduce the conditions at the moment when the ductus arteriosus closes and the blood flow is forced through the lesser circulation, but no measurements of the pulmonary pressure before the onset of respiration in the human fetus have evidently been made (Smith 1946).

The combined effect of inflation and erectile expansion has been studied in an apparatus which is schematically drawn in Plate 4. It should be particularly noted that when using the customary method I, the capillary bed is compressed by the air introduced into the lung and is thus prevented from filling and undergoing erection. For this reason an alternative procedure II in which a negative pressure is used to draw liquid into the capillaries was employed; in this method the compression is avoided and the combined action of respiration and capillary erection is effected.

The aspiration of amniotic fluid has also been imitated in these experiments by introducing india ink into the air stream flowing into the bronchi. We shall call a lung which has been subjected to both inflation and erectile expansion an IE lung, and a lung which has been subjected only to inflation an I lung.

In this work primary atelectasis of the lung has been understood to represent the condition described by Potter and seen in the photomicrographs of Whitehead *et alii.*

The interpretation of the results is based on the possibility of distinguishing between an atelectatic and expanded lung under the microscope.

X. RESULTS

1. *The erectile apparatus of the lung.*

The structure of the lung in primary atelectasis is shown with particular reference to the capillary bed in Plate 5. In the atelectatic state the capillary bed appears to be multiple owing to the extensive folding. When the capillary bed is erected, it is seen to comprise a single layer common to two adjacent air spaces. It is of course obvious that the wall as whole follows the same gross folding as the capillary bed. In agreement with Potter, the structure may be likened to a crumpled sack.

In the light of the presented potential structure, the expansion of the lung may be assumed to take place like that of a crumpled bag when it unfolds. The dilatation may be effected in two different ways:

1) By active erection of the capillary bed with liquid pressure. Plate 6.
2) By inflation of the lung with air, with capillaries passive. Plate 7.

The picture is essentially different depending on whether the capillaries have been actively or passively erected. *The erection of the capillaries with liquid pressure resulted in a condition closely resembling a normal expanded lung.*

Passive erection led to a picture resembling the result of artificial manipulation in which the capillary bed has been thrust aside and subjected to hyperextension. The behavior of the capillaries will be discussed later in connection with clinical cases in which a similar passive hyperextension has occurred as a result of the infant's own respiratory effort.

It can thus be concluded that the capillary bed in the fetal lung is is able to respond to liquid pressure by undergoing erection.

2. *Inflation experiments.*

The reaction of the lung to inflation with air is characteristic and reveals features which may be divided into 1) the changes in the air spaces, Plate 8, and 2) the changes in the capillaries, Plate 9.

The following properties and features characterize the behavior of the air spaces in inflation experiments:

1) The air spaces are globular as if inflated from the inside. The expansion occurs mainly in the proximal air spaces, while the distal spaces remain unaltered.
2) The walls separating the air spaces are thick. Either they consist of tissue that has been compressed by the hyperdistended air spaces or they have undergone no extension.
3) Expansion does not proceed uniformly; hyperextension is frequently observed.
4) Expansion that extends to the respiratory part of the lung may stretch the alveolar walls into thin sheets with red corpuscles from the capillaries accumulated in thicker spots.

The following features characterize the changes in the capillary network.

1) Injected india ink enters the capillaries with difficulty, considerable areas remaining unstained. Smaller unstained areas are seen clearly also on microscopic examination.
2) The capillaries are stretched round the globular air spaces and this stretching prevents their filling. Thus the india ink is deposited mainly on the thicker walls; this corresponds to the accumulation of blood corpuscles in certain areas in stained preparations (see Plate 8, Fig. 6).
3) Capillary sections bulging into the lumens are seldom encountered. (See Plate 12, Fig. 2, and compare it with Plate 11, Fig. 3 and Plate 12, Fig. 1).

In summary it may be stated that the inflation of the lungs through the bronchi by an air pressure difference results in a microscopic picture deviating from the picture of the normal lung. This condition can be effected by model experiments performed post mortem. A similar expansion resembling this microscopically can be produced intra vitam by the infant's own respiratory effort in cases where the capillary erection does not occur or is weak. The microscopic picture of the expansion effected by introducing air is typical and easily recognized.

3. *Erectile expansion and the supporting structure.*

Photomicrographs relating to the erectile expansion experiments are shown in Plates 10 and 11.

Expansion of the lung can be readily effected experimentally by introducing liquid under pressure into the pulmonary artery. The injected liquid does not, however, appear to spread uniformly throughout the capillary bed but leaves some areas unaffected. This is confirmed also on a smaller scale by microscopic observation.

It may be suspected that the picture of the lung dilated by erectile forces seen in the photomicrographs has resulted from the spreading of the liquid only to those parts of the lung that have undergone ''expansion with liquid'' prior to the experiment. The liquid would thus follow the route of least resistance and flow through a previously erected capillary network, leaving unaffected the atelectatic areas which offer a higher resistance. This view is contradicted by the observation that aspirated material is not found in the lumens of the area expanded by the erectile force. The lumens are both void and clear. This is evident also in the photomicrographs in Plates 13, 14 and 15. When the lung has previously undergone ''expansion with liquid'', amniotic fluid, amnion squamae, and extravasal blood are seen in the air spaces.

The pictures of the lungs of premature infants expanded by the infants' own respiratory efforts may have resulted from insufficient capillary erection. It was therefore of interest to determine whether

the erectile force alone is able to expand the lung of a small premature infant. The result of such an experiment is shown in Plate 11.

This picture differs definitely from that produced by artificial air inflation. It differs also from the microscopical picture of the lung of a premature infant that has been expanded by the infant's own respiratory effort (Plate 8, Figs. 3 and 4; Plate 9, Fig 2).

The expanded lung of the premature fetus in question (the fetus weighed only 1300 g) is similar in appearance to a normally expanded lung. The microanatomical details are easily identified. The capillaries have not been stretched by the hyperexpansion of the air spaces, since capillaries bulging into lumens are readily distinguished.

The experimental conditions do not correspond to those prevailing in vivo since the pressure effected in the capillaries is higher than that which a fetus as small as this can presumably produce. Nevertheless the experiment suggests than an insufficient erectile force acting on the capillaries may be one reason for the poor expansion in a living premature infant.

The supporting structure of the capillary network following erectile expansion is clearly shown in Plate 12.

A normal capillary system in an expanded lung resembles closely a rigid tube system. A *stained* capillary system dominates the microanatomical picture of a lung and this shows its importance as the supporting structure of the loose lung tissue. This is not apparent in a lung preparation stained by customary methods where only small round circles reveal the existence of the capillaries.

It was noted above that air introduced under pressure into a lung pushes the capillaries aside and compresses them (Plate 7). This experimental finding is confirmed by Fig. 2, Plate 12, where a similar condition has been effected by the infant's own respiration. A typical feature of the capillaries of a lung inflated artificially with air is that they do not protrude into the lumens. The forms of the capillaries are determined by the degree of stretching. It is highly probable that the stretching obstructs the capillary network and causes impairment of diffusing capacity. If this process involves the whole lung, it is a much more plausible primary cause of cyanosis in the premature infant than a failure in the function of the respiratory center. This possibility will not be pursued further as it is outside the scope of

this study, but it may be noted that the function of the pulmonary capillaries has been considered very little, whereas attention has been mainly directed to the air content of the lung.

Summarizing the effect of liquid introduced under pressure into pulmonary artery we may state the following:

The capillary system of the respiratory part of the excised lung can be readily erected by means of liquid introduced into it under pressure. The resulting microscopical picture resembles that of a normal aerated lung, and the anatomical features are readily identified. The capillary system rendered rigid by liquid forms a framework that supports the respiratory part of the lung.

4. *Combined inflation and erectile expansion.*

Plates 13, 14, 15 and 16 show photomicrographs of the lungs subjected to the combined treatment.

The difference in the expansion of the lungs is clearly seen in the photomicrographs. The picture of the expansion effected by superimposing artificial respiration upon erectile expansion does not differ from that effected by the erectile expansion alone.

A piece of lung excised from the expanded area floats on water. The expansion picture is different when the inflation pressure difference is increased so much that it overweighs the effect of the erectile expansion. It is found that air enters the lung as in the case when it is blown directly through the bronchus. In the photomicrographs this aerated region with its typical globular air spaces is similar in appearance to the hyperextended air spaces effected by air inflation. The first signs of predominating air inflation are seen marked with arrows in Plate 13, Fig. 1. In addition to the uniform area expanded by erectile force in the lower half of the figure, areas containing baglike hyperextended air spaces are seen in both the atelectatic upper region and in a part of the region expanded by the erectile force.

It is probable that when lung expansion occurs in a living infant the conditions may be such that the expanding effect of the respiratory

movements overweighs the expanding effect of erectile force, and a picture similar to that resulting from air inflation is obtained.

On the basis of the above considerations, a premature infant's lung was artificially dilated with both liquid and air as described above. The result is seen in Plate 14. The picture is similar to that of a normally aerated lung and differs from a lung inflated artificially or by the premature infant's own respiratory effort.

The lung condition described as having undergone "expansion with liquid" has been effected by conducting an experiment which yielded the result seen in Plate 16. Whereas india ink was used in the preceding experiment to reveal the penetration of liquid into the capillaries, in the present experiment it was introduced together with air into the bronchus in order to follow the effect of aspirated matter. The experimental conditions were thus chosen to correspond to the status when the fetal blood circulation changes into the adult type while the fetus is still in utero and amniotic fluid instead of air is aspirated into the expanded respiratory part of the lung.

It is seen in the photomicrographs that india ink has spread in both the IE and I lungs up to the terminal air spaces. This shows that the artificial respiration has affected all parts up to the alveoli. The I lung, however, has not undergone expansion. In the IE lung an expansion resembling the normal has occurred, the air spaces being filled with india ink or air. This result can hardly be explained in any other way than by assuming that the liquid pressure has acted on the capillary network and thus produced expansion of the lung.

If the result of this experiment can be applied to the processes taking place in vivo, the significance of the via dextra in preventing expansion in fetal life is obvious.

In summary we may conclude that artificial respiration in combination with liquid pressure acting through the pulmonary artery effects in an excised lung an expansion, the microanatomical picture of which closely resembles that of a normally aerated lung. The picture is similar to that effected experimentally by introducing only liquid under pressure into the pulmonary artery. When artificial respiratory movements are added to the erectile expansion, so much air may enter the lung that it floats on water.

XI. DISCUSSION

When considering the results of the experiments, it should be noted that the experiments have dealt only with a mechanical process which can be effected provided we have a system of folded tubes (the erectile apparatus of the lung) and are able to produce a liquid pressure within the system. The process cannot thus take place in the living organism if the necessary hemodynamic conditions do not exist or if the erectile apparatus is defective or lacking.

From the studies of DAWES we know that the vascular resistance is initially pronounced in a newborn lamb, the pulmonary pressure being temporarily as high as 80 mm Hg. Hemodynamic conditions thus exist which are able to effect capillary erection.

As far as the erectile apparatus is concerned, there is hardly any doubt that it is fully developed in the full-term infant. With immature infants this may not be the case. In the latter, owing to developmental factors, there is no folded alveolar wall that may be expanded and the underdeveloped capillary network is unable to effect erection of the lung. The nonexistence of the erectile apparatus or its incomplete development is probably the reason why erection could not be effected in the lungs from fetuses, eight in number, weighing 500 to 800 grams.

Capillary erection can however be easily produced in the lung of a full-term fetus. The same result was obtained by KRAFKA in a similar model experiment, which, however, had another purpose.

It seems that it is not possible to obtain ideal lung material for such experiments from human sources. The fetus usually dies as a result of a condition which mostly leads to "expansion with liquid". In lungs of such fetuses, artificial erection tended to add to the expansion that had already occurred. These cases have not been described in this publication; the two pure primarily atelectatic lungs that have been described were from fetal lambs.

The degree of expansion that can be effected artificially is determined by several factors. The specimen shown in normal size in Plate 15 is presented to give the reader an idea of the average extent of the expansion (light areas) seen in the photomicrographs in the same plate. Conditions limiting the artificial expansion are the immaturity of the lung, the presence of aspirated material in the air spaces, and capillaries occluded with blood cells.

Several additional factors exist in the living lung that may influence the capillary erection and which cannot be reproduced in dead material. These factors are connected with the vital reactions of the pulmonary vessels. For example, WEARN *et alii* (1934) have studied the capillaries in the living lung with the microscope and have observed that they alternately disappear and become filled with blood. The variation of the pulmonary pressure caused by high and low oxygen concentrations has been described by EULER and LILJESTRAND (1947). These vital reactions cannot be imitated in dead material and are the reasons why there is very little point in making quantitative measurements. For this reason I have been satisfied to show that the erectile apparatus actually exists and that it also can be caused to function artificially.

The information required for an understanding of the processes involved had to be sought in earlier studies with other objectives. It was not, however, possible to determine the authors' opinions and views as far as they concern the present problem from these studies. It may be nevertheless be permissible to apply the facts that have come to light in the present study to earlier observations.

Erectile apparatus of the lung. LELONG and LAUMONIER have stated that in a group of premature infants in the seventh month of gestation who survived from 1 to 3 weeks the walls of the air spaces were bordered with capillaries which were arranged in several networks. When the infant survived for 2 months, the walls were thin and composed of a single capillary network. These descriptions possibly refer to a nonerected and erected capillary network, respectively. The corrugated nature of the walls of the air spaces is apparent from the work of AHVENAINEN (1948) who observed that the walls are tense in the aerated but corrugated in the atelectatic lung.

Inflation experiments when capillary erection does not occur. Many authors, among them POTTER, have observed that it is not possible to expand the lung of an infant artificially in the manner the respiration of the infant does. The lung can be expanded by means of artificial respiration apparatus if this is done according to the Day impulse principle, but the infant does not effect the expansion according to this principle.

The pathological - anatomical picture of the lung which has been artificially insufflated and the similar picture of the lung in the premature infant have been described by POTTER in the following words: ''The artificial introduction of air or oxygen causes a greater irregularity in expansion than brought about by normal breathing. The proximal air spaces often become distended into globular saclike structures while more distal spaces fail to expand and become secondarily collapsed as a result of pressure from the parts containing air. Such an appearance in the mature infant is diagnostic of artificial resuscitation. In a premature infant of 1000—2000 grams a similar picture may be produced by the infant's own inspiratory efforts.''

Also the observations of MACKLIN relating to the imbalance between the distention of the alveoli and the vascular bed may in the present writer's opinion be explained by the absence of capillary erection. The photographs in Figs. 1—4 of Plate 8 illustrate MACKLIN's factor A and that in Fig. 5 his factor B.

The function of the capillary erection. The observations that a lung may expand although no outside connection through the larynx has never existed can be readily explained by capillary erection.

The lung tends to contract owing to its elasticity, surface tension being possibly a contributory factor, unless some force does not oppose the contraction. In the adult lung the opposing force is the negative pressure in the pleural cavity and friction. Since there is no negative pressure in the pleural cavity of the newborn, the most important factor that keeps the residual air in the adult lung is lacking in the newborn. The erected capillary structure provides an explanation for the ''elastic pull'' which maintains the respiratory part of the lung upright and holds the residual air within the lung.

The relation between the initiation of respiration, the capillary erection and the change in the fetal blood circulation. This aspect has not been investigated. Our present knowledge may be summa-

rized as follows. KENNEDY and CLARK have observed in experiments with animals that respiration may begin first and closure of the ductus arteriosus may occur later, but nevertheless immediately after delivery has taken place. From the viewpoint of capillary erection, it seems that the change in the blood circulation from the fetal to the adult pattern is a result of closure of the fetal channels, whereupon the blood is forced to flow through the lesser circulation. The latest investigations, however, appear to suggest that the ductus does not close immediately following birth. The change in the circulation must then be effected by a process other than the closure of the ductus. One possible factor is the negative pressure resulting from the respiration, but only investigations performed on living material can provide an answer to this problem.

XII. SUMMARY AND CONCLUSIONS

The opinion is presented that a previously uninvestigated factor, *capillary erection,* plays an important part in effecting lung expansion in the newborn infant. The respiratory part of the lung is the apparatus in which capillary erection occurs and the erection is effected by an increase in liquid pressure in the pulmonary artery.

The opinion is based upon histological investigations and upon the following model experiments:

I. The architecture of primary atelectasis has been studied by examining the general course of the capillary network which has been rendered visible by injecting india ink into the pulmonary artery. The findings are in agreement with those of POTTER who has stated that a lung in primary atelectasis may be compared to a crumpled sack. In this case atelectasis has been understood to mean the architecture of the fetal lung at term before any aeration or expansion has occurred.

II. The opening-up of the atelectatic lung is considered to involve its extension as a result of the active erection of the capillary network. Evidence in support of this opinion has been obtained by studying various stages of expansion in the same preparation. Thus the straightening-out of the crumpled sack effects the expansion of the respiratory part of the lung.

III. Expansion experiments have been performed on lungs of stillborn human and lamb fetuses. The following possibilities have been examined:

1. Lung expansion effected by an air pressure difference in the respiratory passages. This method is termed air inflation.

2. Lung expansion effected by liquid pressure in the capillary network. This method is termed erectile expansion.
3. Lung expansion effected by air inflation and erectile expansion concurrently.

The results of the expansion experiments show that the air inflation effects an expansion which is characterized by a microscopical picture showing globular saclike hyperdistended air spaces primarily in the distal conducting part of the lung. A similar condition of the lung results from the child's own respiratory efforts in cases where the erectile forces in the capillaries have been weak or nonexistent.

Liquid pressure acting through the pulmonary artery produces in the respiratory part a condition which exactly corresponds in its microanatomical features to a normal aerated lung.

Air inflation and erectile expansion together produce a picture which is similar to that effected by erectile expansion alone. By increasing the air pressure difference it is possible to change the balance between the air inflation and erectile expansion so that features appear in the microscopical picture which are typical of a lung expanded by air inflation alone.

Both when effected experimentally or by the child's own respiratory movements, air inflation appears to hinder attainment of the normal structure by the capillary network by stretching the capillaries and by forcing them to conform to the hyperdistention of the air spaces. The stretching of the capillaries appears to prevent their bulging into the adjacent air spaces.

XIII. PLATES

PLATE 1. THE ANATOMY OF FETAL HEART.

FIG. 1. Schematic drawing of the heart of the fetal lamb according to Barron.

FIG. 2. Schematic drawing of the heart of the human fetus according to Keen.

FIGS. 3—4. Inlet of the inferior vena cava in a full-term human fetus. Photographed by the author.

Plate 1.

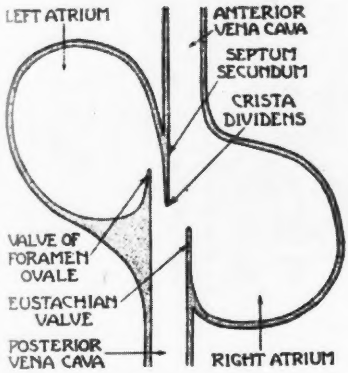


Fig. 1

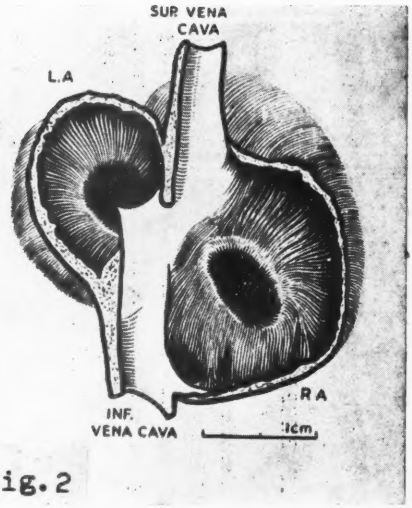


Fig. 2

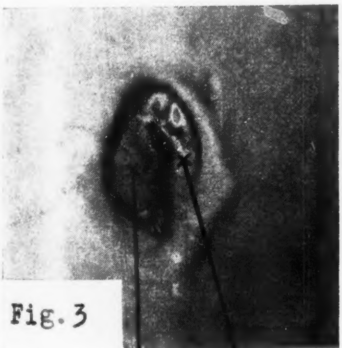


Fig. 3

Eustachian valve

Valve of foramen ovale

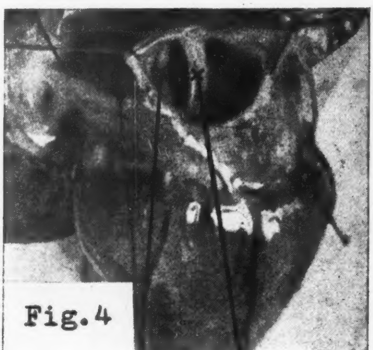


Fig. 4

Crista dividens

Valve of foramen ovale

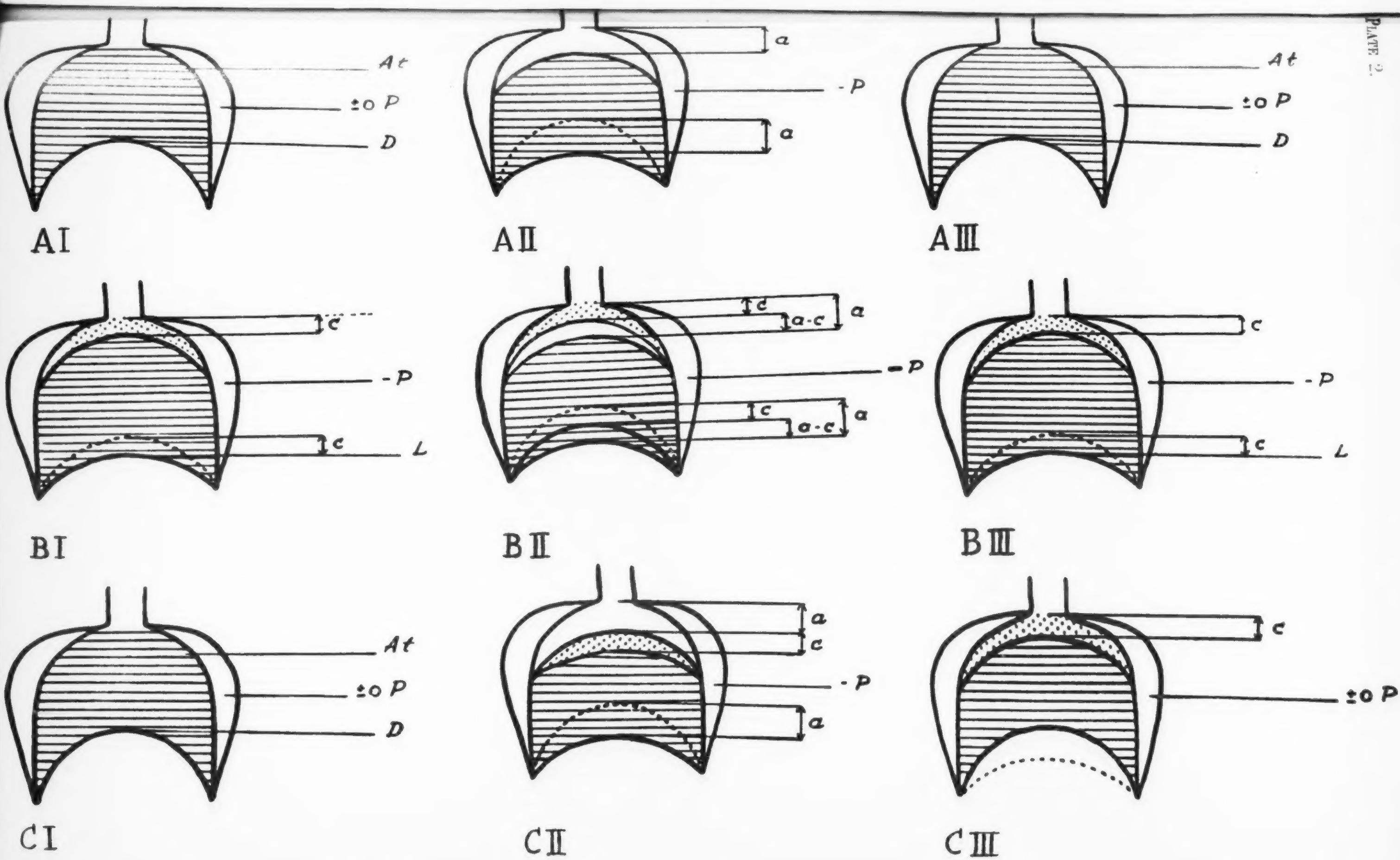
PLATE 2. THE PHYSICS OF RESPIRATION.

A I illustrates the initial state where the lungs are atelectatic (At) and the summit of the diaphragm is in the upper position (D). The pressure in the pleural cavity is zero. A II illustrates the conditions during the first inspiration. The diaphragm is drawn down which effects the flow of air (a) into the lung. A negative pressure prevails in the pleural cavity during the inspiration. A III illustrates expiration. Since expiration is a relaxation, the diaphragm returns to its initial position and the air that has been inhaled is forced out. The negative pressure disappears from the pleural cavity.

Let us now suppose that all the inhaled air is not completely expelled, and a small residual volume air (c) remains in the lungs. This is illustrated by B I. This is mechanically possible, but the diaphragm must then remain contracted in a lower position than in A III. A slight negative pressure will also remain, and the residual air will form a part of the vital capacity. The state B I will then be the initial state preceding the next inspiration B II. The contraction of the diaphragm will begin at the level L and the diaphragm will be able to move only the distance a-c. The next expiration B III will resemble that shown in B I.

The respiration as it occurs according to known physiological facts is illustrated in figures C I—C III. C I shows the initial state. C II illustrates the first inspiration during which the summit of the diaphragm moves the maximum distance and a volume of air (a) equal to the vital capacity is inhaled. The total air volume in the lungs comprises, however, in addition to the vital capacity a residual volume (c) produced by some other process. A negative pressure prevails in the pleural cavity during the inspiration. Complete relaxation accompanies expiration leading to C III, the diaphragm returns to the initial position and the negative pressure disappears, but a residual volume of air (c) remains in the lung.

PLATE 2.



AI AII AIII

BI BII BIII

CI CII CIII

PLATE 3. GENERAL SCHEME OF A PRIMARY LOBULE AFTER MILLER.

B. Bronchiolus respiratorius, which divides into two ductuli alveolares, only one of which is carried out to its final subdivisions. ALV'., Alveoli scattered along the bronchiolus respiratorius and the ductuli alveolares.

A. Three atria. S. AL., Sacculi alveolares. ALV., Alveoli pulmonum P, Pleura pulmonalis. 1. Arteria pulmonalis. 2. Branches of the arteria pulmonalis which are distributed to the bronchiolus respiratorius and ductulus alveolaris. 3. Vena pulmonalis, with its branches of origin indicated at 6, 9, 10. 4. Lymphatics. 5. Arteria bronchiales.

PLATE 3.

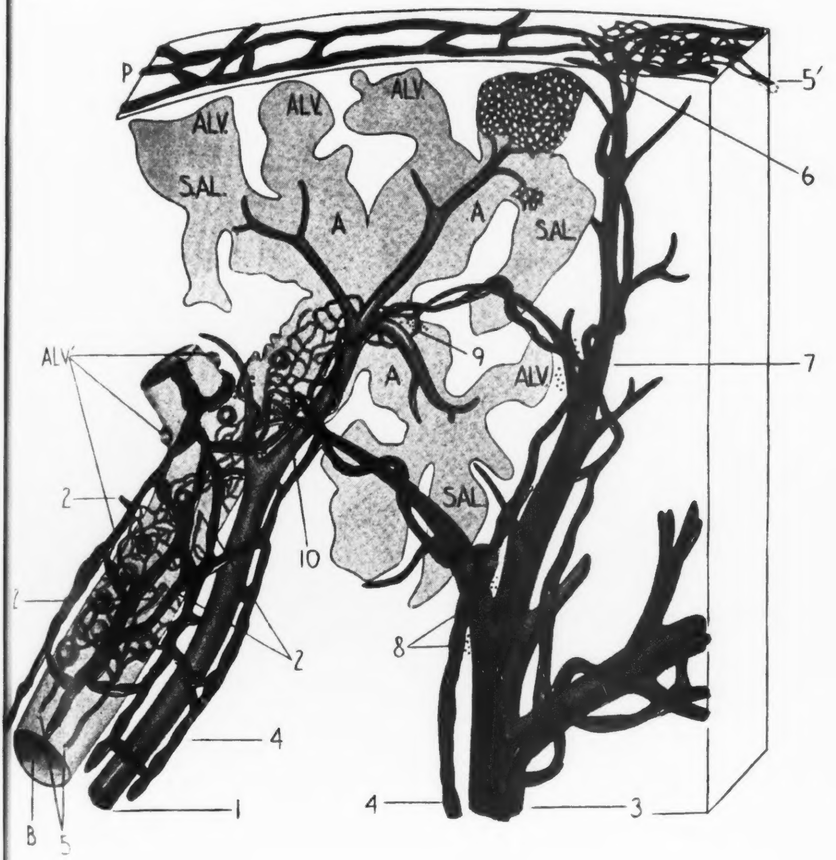


PLATE 4. THE EXPERIMENTAL ARRANGEMENT.

Schematic drawning illustrating air inflation and combined inflation and erectile expansion experiments.

For a detailed explanation, see text, p. 38.

PLATE 4.

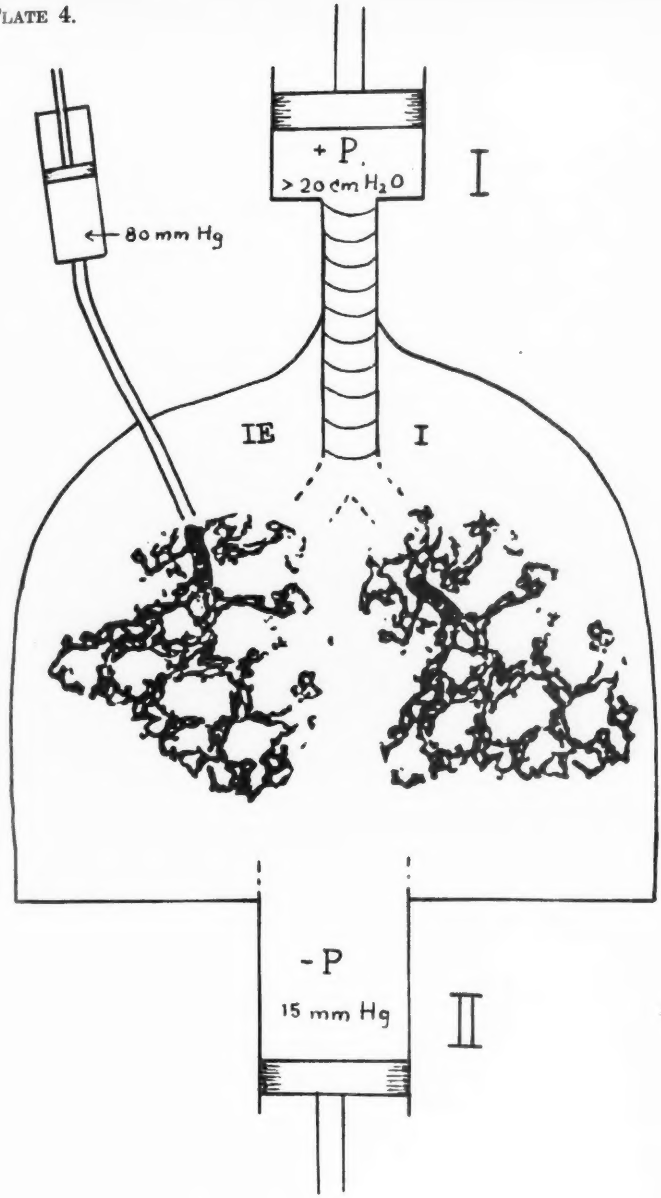


PLATE 5. "THE CRUMPLED SACK." PRIMARY ATELECTASIS.

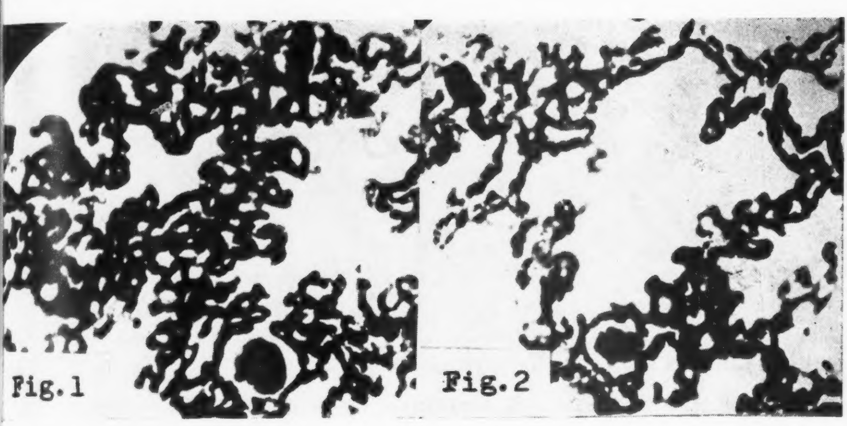
The capillaries of an ether-fixed lung have been rendered visible by injecting india ink. The general course of the capillary bed is drawn below in simplified outline by disregarding the secondary folding.

FIG. 1. Almost fully atelectatic condition.

FIG. 2. Partly expanded state.

Magnification x 270.

PLATE 5.



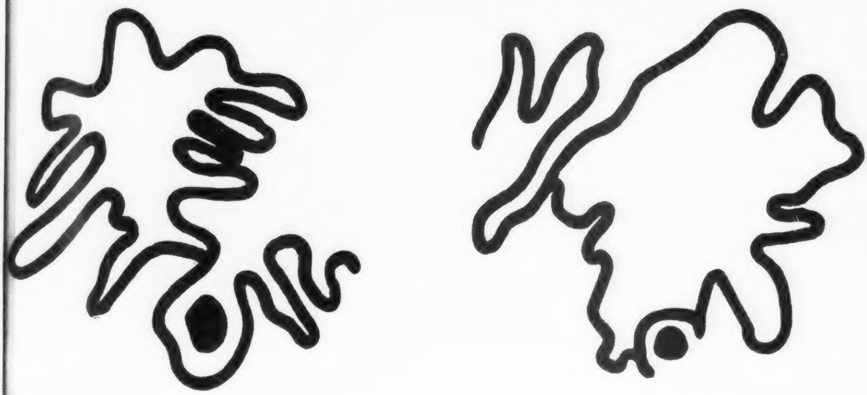


PLATE 6. ACTIVE CAPILLARY ERECTION.

Series of capillary erection processes showing opening-up of air spaces in the respiratory part of the lung. Different regions of the same ether-fixed lung which was subjected to a liquid pressure of 80 mm Hg through the pulmonary artery. Series A, sagittal sections through a primary lobule below the pleura. Series B, transverse sections.

Magnification $\times 270$.

LATE 6.

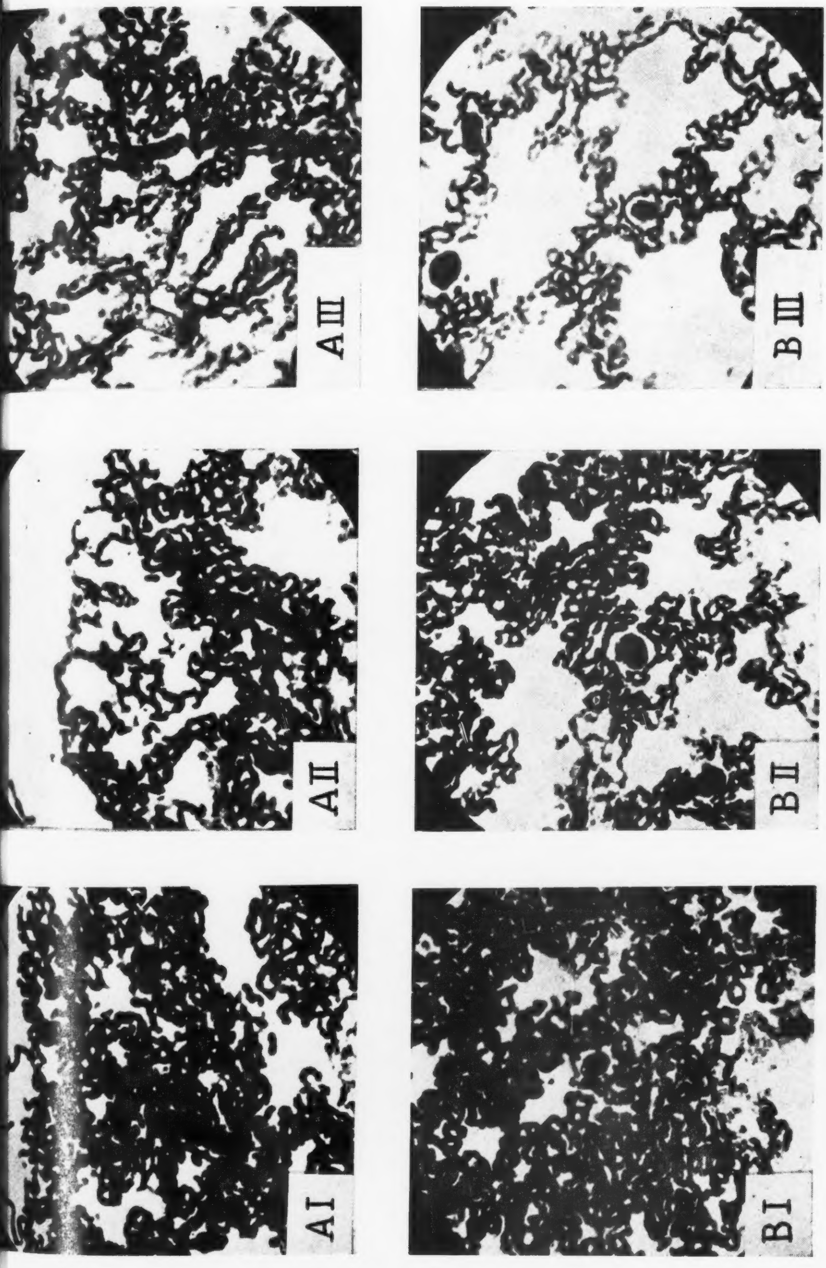


PLATE 7. AIR INFLATION WITH CAPILLARIES PASSIVE.

Ether-lung into which air has been introduced by negative external pressure (Plate 4, method II) followed by india ink injected through the pulmonary artery to make the capillaries visible.

PLATE 7.

PLATE 8. AIR INFLATION EXPERIMENTS.

The changes in the air spaces.

FIG. 1. Lung of full-term infant which has been inflated with air.

FIG. 2. Lung of a full-term infant which has been insufflated intra vitam.

FIGS. 3 and 4. Lung of a premature infant weighing 1350 g. Expansion effected by the spontaneous respiration of the infant. The child lived seven hours.

FIG. 5. Lung of a full-term infant that died from profuse hemorrhage on the third day after firth.

FIG. 6. A detail of the lung of Fig. 2.

Magnification: Figs. 1—5 ×60, Fig. 6 ×270.

LATE 8.

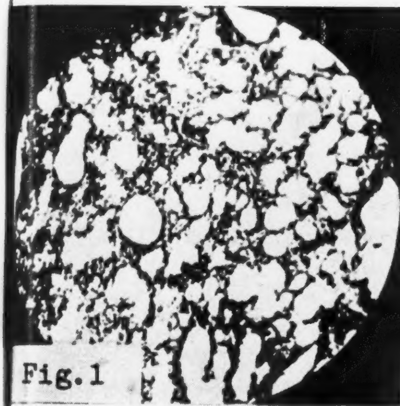


Fig.1

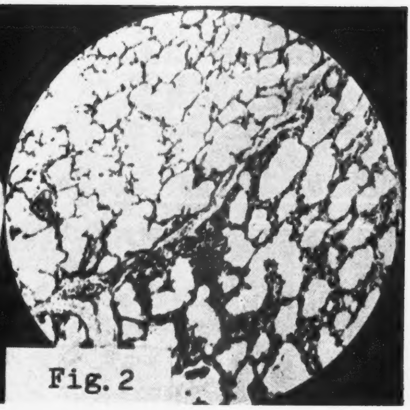


Fig.2

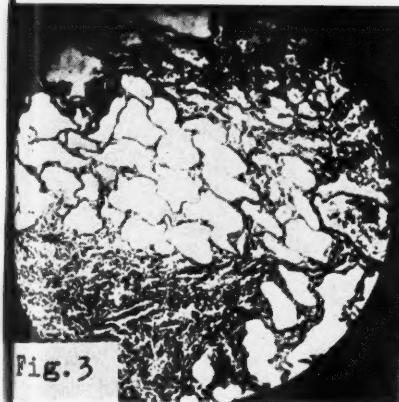


Fig.3

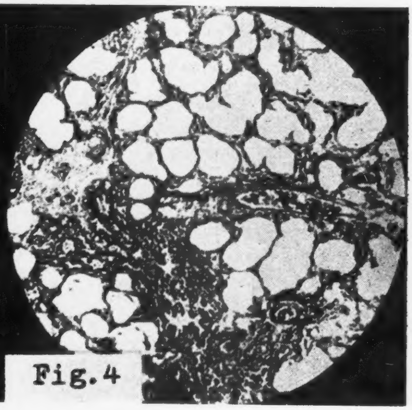
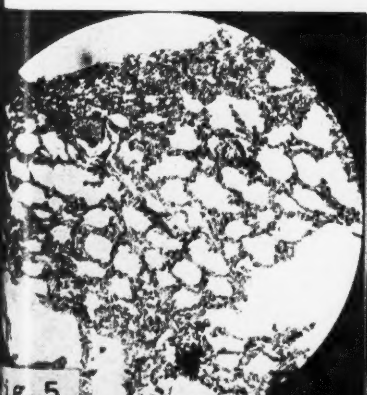


Fig.4



ig.5

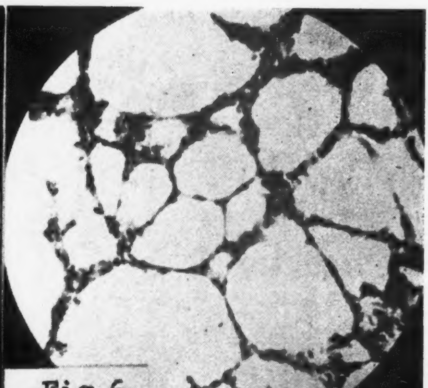


Fig.6

PLATE 9. LUNG EXPANSION WITH WEAK CAPILLARY ERECTION.

The changes in the capillaries.

FIG. 1. The other lung of the melena case (Plate 8, Fig. 5.)

FIG. 2. Lung of an immature infant weighing 1220 g who lived one day. Capillaries injected with india ink. Tissues unstained. Magnification × 60.

PLATE 9.

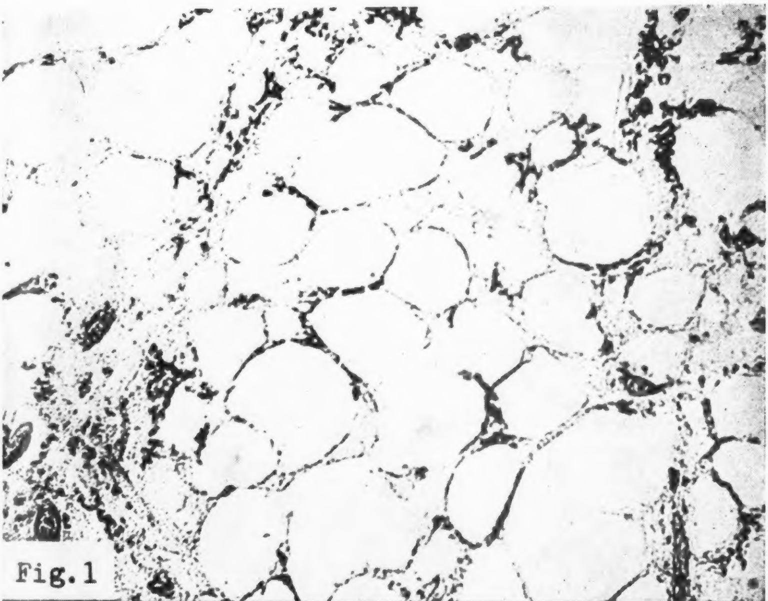


Fig. 1

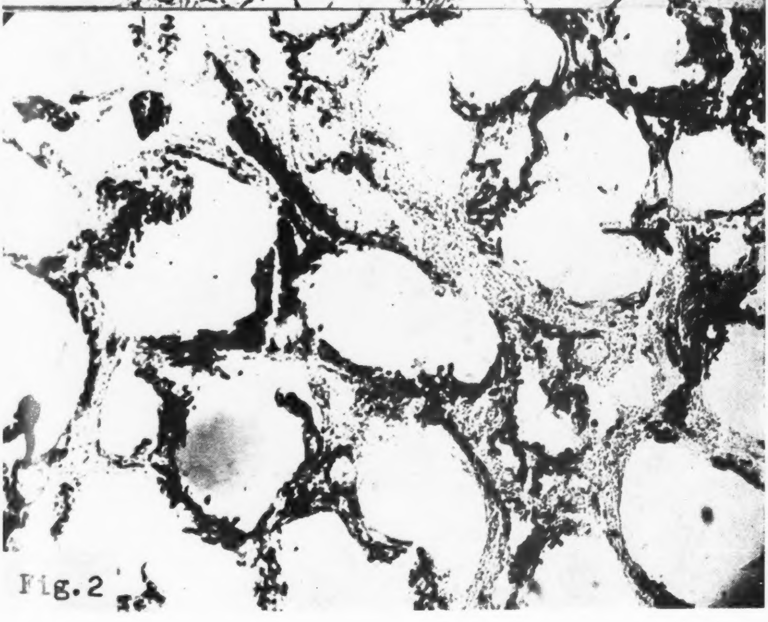


Fig. 2

PLATE 10. ERECTILE EXPANSION.

FIG. 1. Lung of a full-term infant which has been deep-frozen to hemolyze the blood cells. India ink injected under a pressure of 80 mm Hg into the pulmonary artery has entered the capillaries and effected expansion.

FIG. 2. A picture showing a region of the same lung in the original atelectatic state. India ink has not penetrated up to the capillaries and hence no expansion has resulted.

Magnification × 60.

PLATE 10.

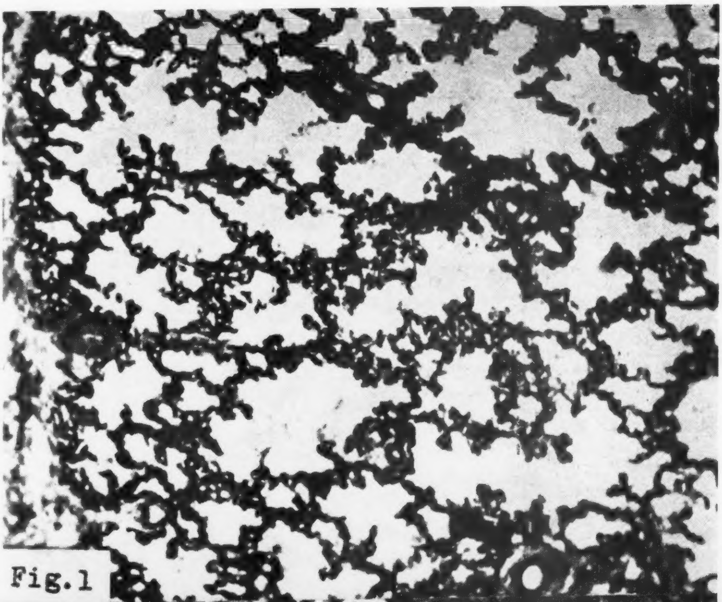


Fig. 1

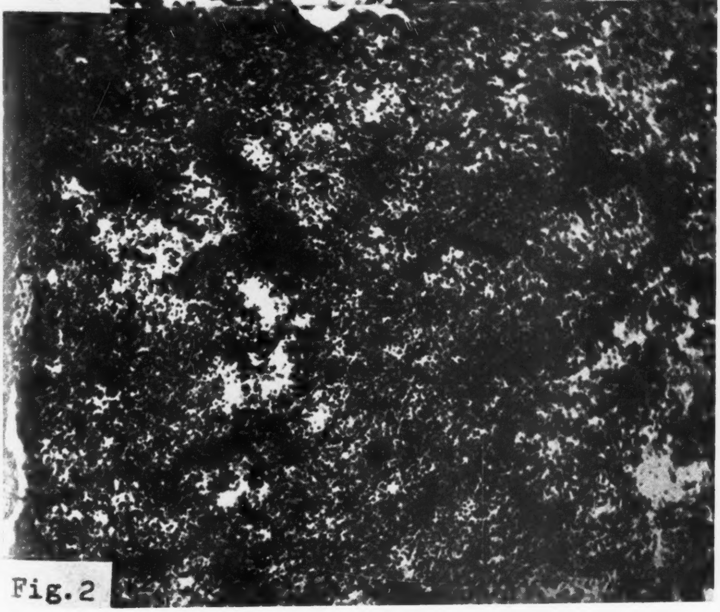


Fig. 2

PLATE 11. ERECTILE EXPANSION OF PREMATURE LUNG.

Lungs of a premature fetus weighing 1300 g.

The lungs have not been prepared with ether or by deep-freezing.

FIG. 1. Lung expanded by introducing liquid under 80 mm Hg pressure.

FIG. 2. Lung in the original atelectatic state.

FIG. 3. A detail of a region in Fig. 1. Capillary cross-sections are indicated by arrows.

Magnification: Figs. 1 and 2, ×60; Fig. 3, ×270.

PLATE 11.

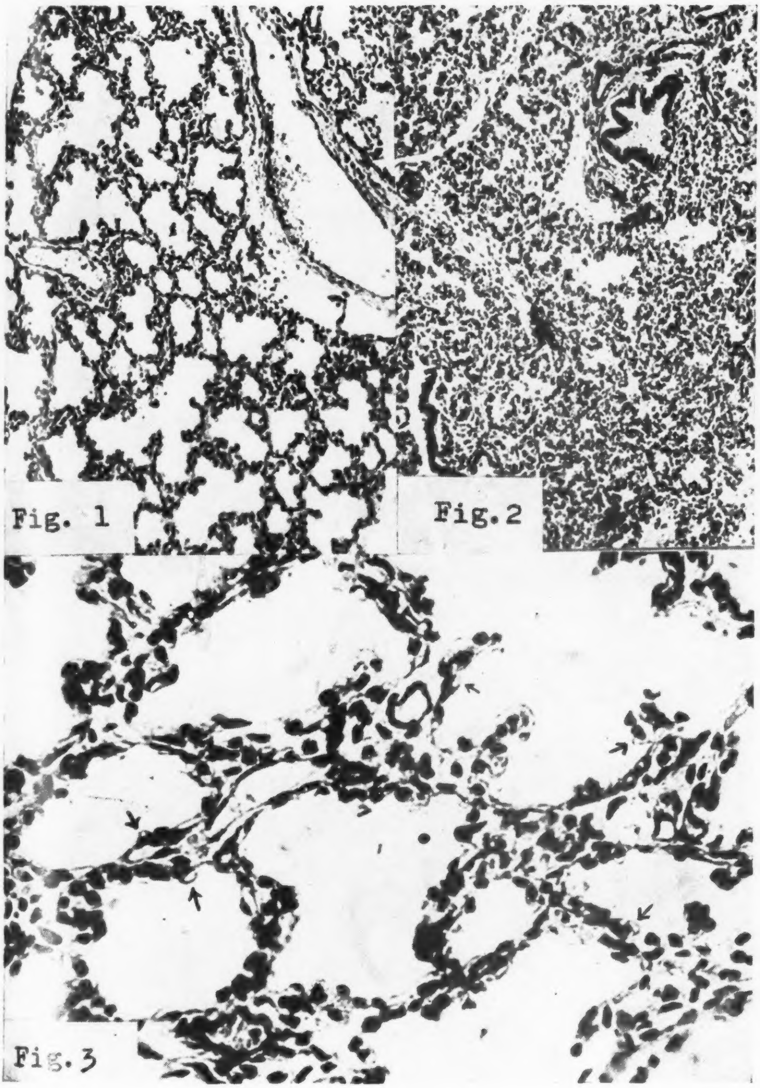


PLATE 12. SUPPORTING STRUCTURE.

FIG. 1. Capillary network in the lung of a fetus weighing 1550 g. Expanded by erectile force. Note the luxuriant growth of capillaries bulging into the air spraces. The network suggests that it functions as a supporting structure of the respiratory part.

FIG. 2. Capillary network in the lung of a immature baby weighing 1220 g which lived one day. The stretched and compressed capillary network does not bulge into the adjacent air spaces and suggests impaired diffusing capacity.

Plate 12.

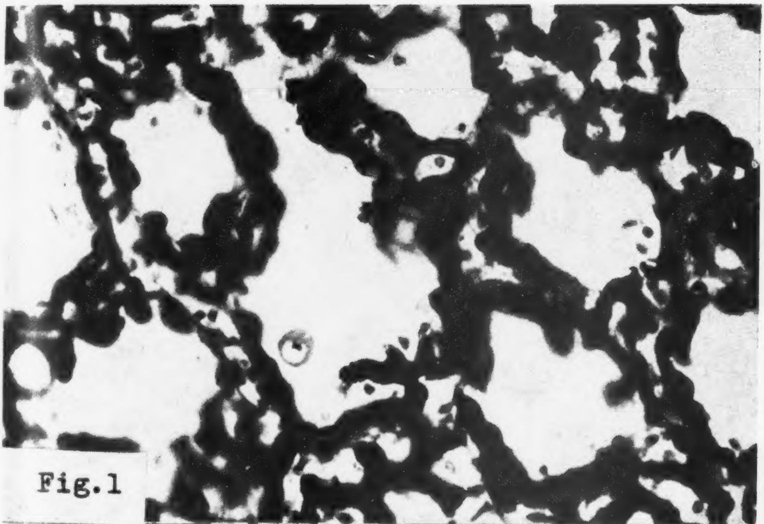


Fig.1

Fig.2

PLATE 13. COMBINED INFLATION AND ERECTILE EXPANSION.

Ether-fixed lung excised from a stillborn fetus weighing 3200 g.

FIG. 1. IE lung. Magnification only ×10 to give a general impression.

The diagonally located thick blood vessel divides the lung area into two parts. The upper part contains no india ink in the capillaries and is in the atelectatic state.

The lower part contains india in the capillaries and is characterized by expansion.

FIG. 2. Detail of the IE lung. At the left no india ink has penetrated into the capillaries. At the right the india ink has filled the capillaries.

Magnification: ×60.

LATE 13.

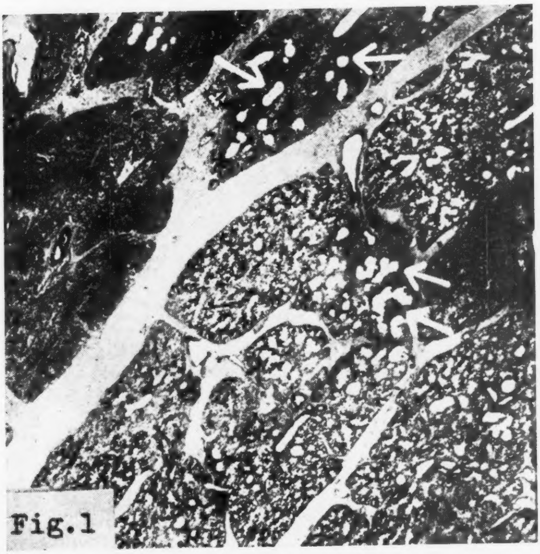


Fig.1

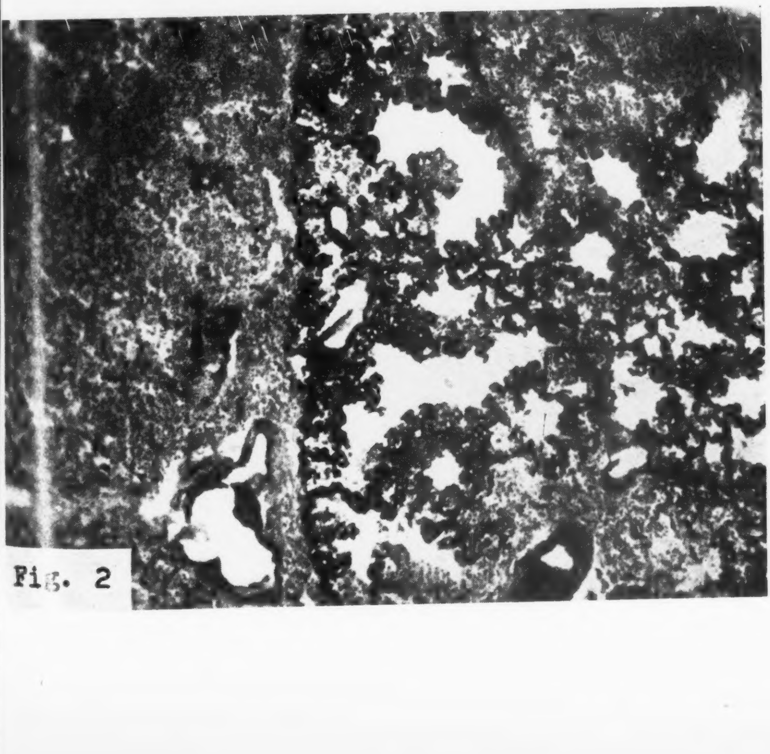


Fig. 2

PLATE 14. COMBINED INFLATION AND ERECTILE EXPANSION IN PREMATURE LUNG.

Lungs of a premature fetus weighing 1880 g. The lungs were not immersed in ether or subjected to deep freezing.

FIG. 1. IE lung. Macrodex containing no india ink has been injected into the pulmonary artery.

FIG. 2. I lung. Original atelectatic state.

Magnification ×60.

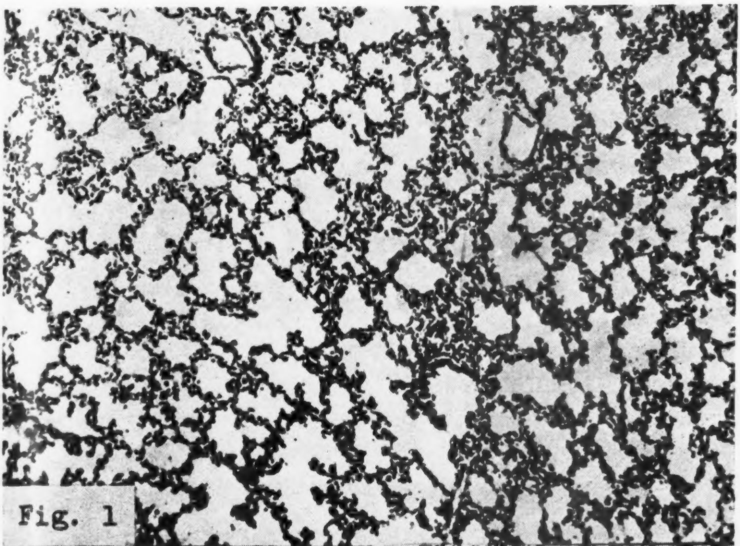


Fig. 1

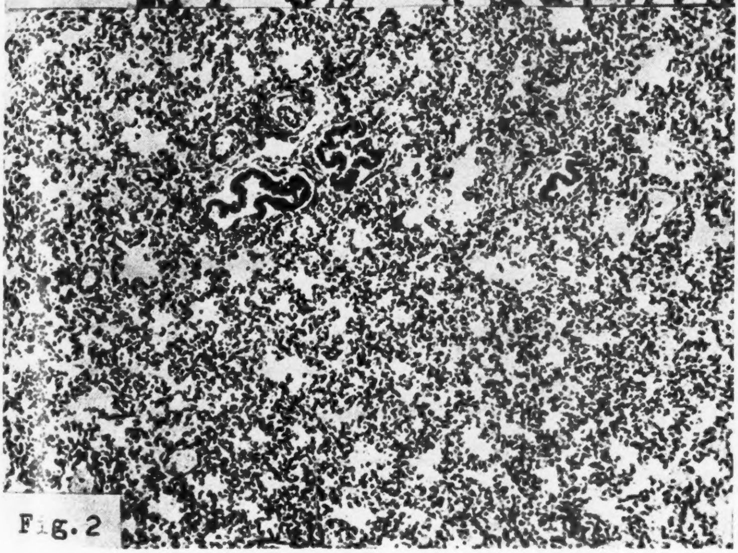


Fig. 2

PLATE 15. COMBINED INFLATION AND ERECTILE EXPANSION IN A LAMB FETUS.

The erectile force has been effected in this case by introducing radio-opaque.

FIG. 1. IE lung. Magnified photograph of round pale area seen in the photograph of the slide in the right upper corner into which radio-opaque has penetrated.

FIG. 2. I lung.

Magnification ×60.

PLATE 15.

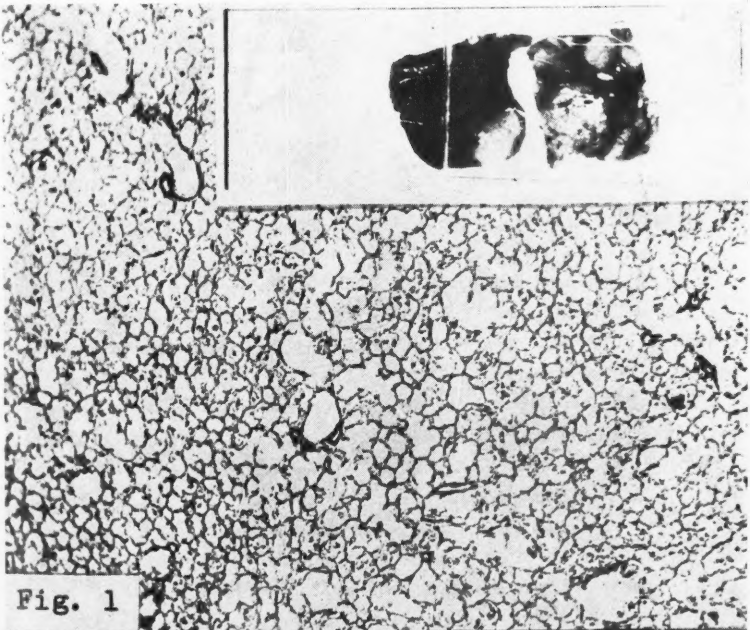


Fig. 1

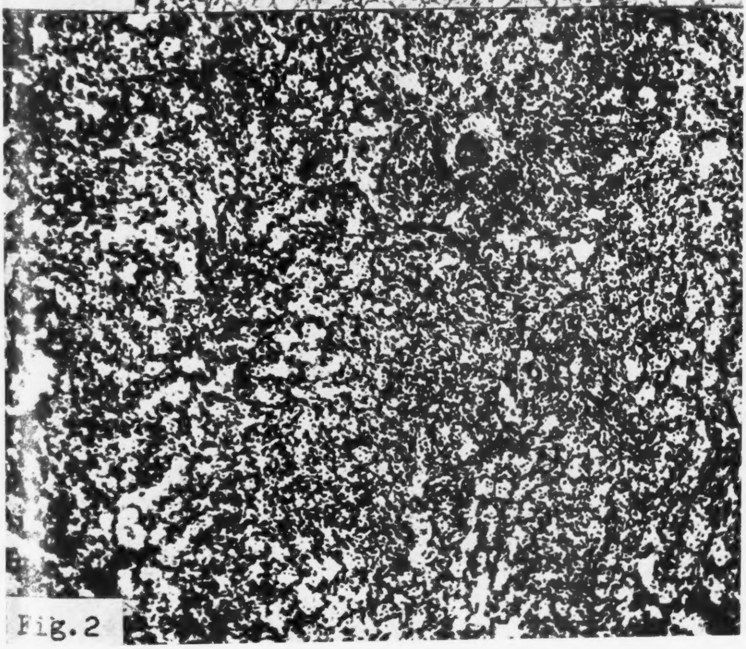


Fig.2

PLATE 16. IMITATION OF "EXPANSION WITH LIQUID".

Lung of a stillborn fetus weighing 2600 g which had died about one week prior to delivery. The blood has partly autolyzed. In order to imitate aspiration of amniotic fluid both india ink and air were introduced simultaneously into the trachea.

FIG. 1. IE lung. The upper darker area shows air spaces into which india ink has entered: "expansion with lipuid". The lower part has become filled with air.

FIG. 2. I lung. The dark lung areas in which the india ink has entered up to the terminal air spaces have not undergone any changes. The picture illustrates the result of fetal respiratory movements when lung expansion does not occur owing to the absence of capillary erection.

Magnification: ×60.

Plate 16.

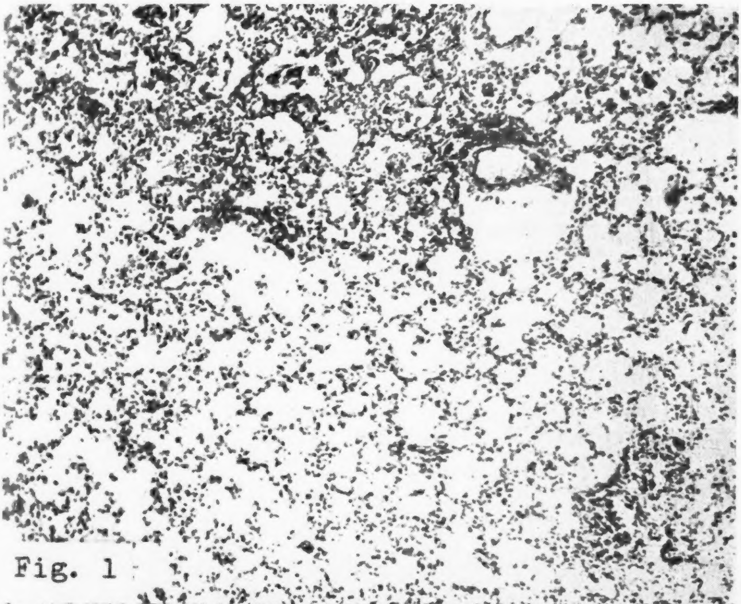


Fig. 1

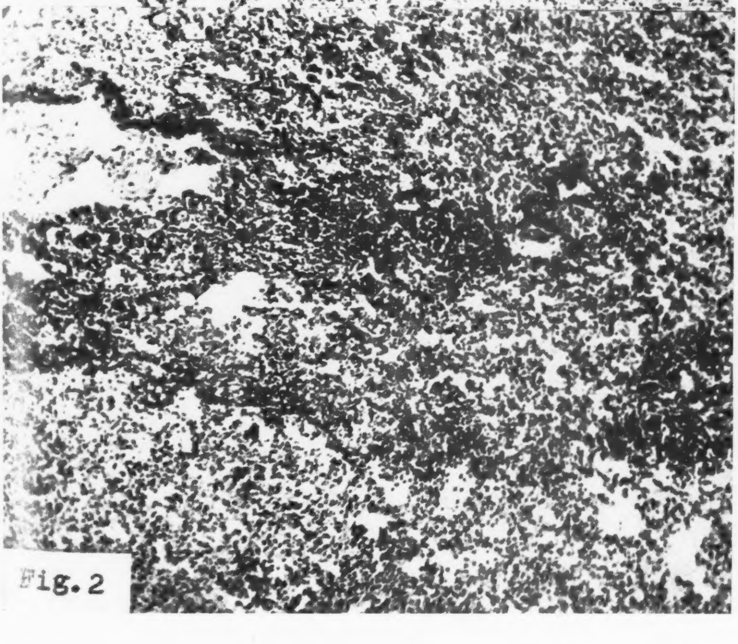


Fig. 2

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43
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48
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54
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64
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72
76
77
79
80
81
83

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FROM THE DEPARTMENT OF MEDICAL
PHYSICS, KAROLINSKA INSTITUTET,
STOCKHOLM

BIOPHYSICAL ANALYSES OF THE FORMATION AND STRUCTURE OF HUMAN FETAL BONE

A MICRORADIOGRAPHIC AND X-RAY CRYSTALLOGRAPHIC STUDY

BY

GÖRAN WALLGREN

STOCKHOLM 1957

TRYCKERI BALDER AB • STOCKHOLM 1957

To my parents

II

I

V

VI

VII

Table of Contents

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I. General Introduction

The very rapid technological advances of the past twenty years have provided a tremendous impetus to biological and medical research. New, and highly sensitive methods have become available during this time, which permit a rational approach to a multitude of problems relating to structure, growth, and metabolism in biological systems. In fact, the application of these modern techniques of research to biological materials has already brought to light many important structural and functional features, the existence of which was previously completely unsuspected, or was at best only speculated upon.

The stimulating effect upon biological research of modern technical developments is perhaps nowhere better reflected than in the recent great advances which have been achieved in our understanding of bone physiology. Here, the use of a wide variety of newly-developed analytical methods has markedly enriched our knowledge both of bone structure and of bone function.

Of particular importance to our recent progress in this field have been the various biophysical methods of analysis. Thus, x-ray diffraction studies of the mineral compartment of bone have allowed a deeper insight into levels of structural organization far lower than those which can be appreciated by ordinary microscopy. Diffraction techniques, together with recent electron microscopic investigations, have combined to provide us with our current concepts of the ultrastructure of bone, including the molecular structure of the crystallites, their size, and their spatial relationship to the organic matrix.

Another biophysical method which has contributed a large mass of information in the study of bone, especially with regard to bone metabolism, is the radio-tracer technique. Radio-isotopic investigations of bone under a variety of physiological conditions have shown most convincingly the striking and highly significant role played by the skeleton in bodily homeostasis. These investigations have demonstrated, above all, that the skeleton is a dynamic physiological unit, of the utmost importance to the

normal function of the body as a whole, and not (as was previously thought) simply a structure whose prime functions are those of providing support for the body and a protective sheath for the bone marrow.

A third biophysical method which has been of considerable value to studies of mineral distribution and mineral aquisition on a quantitative level is that of x-ray microradiography. This technique permits the determination of extremely small amounts of bone mineral in structures of microscopic dimensions, and possesses a high degree of precision. It has been used particularly in studies of normal and diseased adult bone, but has also provided very valuable information regarding bone growth, and has shown the direct relation between age and mineral content in microscopic bone structures. Moreover, in conjunction with radio-tracer studies, it has demonstrated the dominant role played by the young, not fully mineralized bone, in the dynamics of skeletal metabolism.

The greatest share of our present knowledge of bone, however, is derived from studies of the adult tissue. Its structural aspects have been elucidated in particular detail. But from the relatively large body of information concerning the metabolic aspects of the skeleton, it seems that it is the young, or immature bone rather than the adult bone which has the most important role. Logically, then, interest is now turning toward characterizing those features of young bone which make it differ in respect to metabolism from the adult tissue. Efforts at characterizing these differences must *a priori* be directed toward correlating structural and functional features during growth.

The dynamics of skeletal growth are in all probability appreciated best during fetal development. For throughout intrauterine life, the absolute rate of growth of the skeleton, as indeed of all tissues, is at its maximum. Consequently, structural and functional changes associated with growth are likely to be most pronounced and readily measurable at this time.

Much of our knowledge of the structure and metabolism of human fetal bone has been derived by inference from studies of post-natal, rapidly growing bone. However, a certain body of information dealing specifically with fetal bone is available in the literature. Textbooks of embryology and histology provide a comprehensive and detailed picture of the histological changes associated with fetal bone development in the human (79, 87, 121, 122). A number of investigations have concerned themselves with particular features of skeletal development, including the time and sequence of appearance of ossification centers, as well as special structural features associated with the development of individual bones (10, 30, 49, 57, 70, 80, 81, 89, 95, 116, 117).

Histochemical and biochemical investigations have been performed on post-natal human bone, under both normal and pathological conditions,

and in combination with studies of other species have provided considerable information regarding the complex biochemical phenomena which are associated with the normal process of mineralization, or with disturbances in it (14, 32, 91, 115). Similar studies of fetal bone, although few in number, seem to suggest that similar patterns exist during intrauterine life (13, 48, 68, 90, 100, 114).

Chemical analyses of human fetal bone have been limited to the study of the mineral compartment. It has been shown that during fetal life, the water content of fresh fetal bone decreases, as does the content of magnesium, sodium and chlorine in ashed bone, while the calcium to phosphorus ratio remains constant (112, 113). The citrate content increases progressively during development (88). Premature infants whose mothers suffer from inadequate nutrition demonstrate a decreased calcium and phosphorus content compared to premature infants of adequately fed mothers (118). In a comparative study of the mineral component of fetal skull bones ranging in age from 28 weeks to full-term, it was shown that both the calcium and carbonate content increase with age, while the phosphorus and collagen content do not change appreciably (78). The increase in calcium and carbonate was considered to be responsible for the increase in hardness of the bone which was observed in the older specimens.

Since the first experiments on transplantation and tissue culture of human fetal bone in 1926 (109), a large body of literature has appeared on this subject (for a summary of the current status of this research, the reader is referred to reference 47). These studies have demonstrated not only the great utility of these methods for experimental investigation of the effects of various physiological and pharmacological stimuli on bone growth, but they have also demonstrated the remarkable potential of fetal bone to differentiate and grow, even when deprived of its natural environment.

From the data presented in the previous paragraphs, it is evident that our knowledge of human fetal bone, compared to that available regarding adult bone, is relatively meager and requires considerable further experimental study. The present dearth of information is due in part, of course, to the difficulty attendant on obtaining experimental material, and in part also to the small size of the fetal structures. Equally important, however, is the fact that the methods employed in the past for making analyses and measurements of fetal bone are themselves limited in their sensitivity. Thus, microscopic examination, whatever its objective, has been limited until recently by the ultimate resolution of the light microscope. By the same token, chemical analyses have suffered from the fact that chemical methods are not sufficiently sensitive to give accurate results on the relatively small amounts of fetal bone usually available for study.

Earlier in this section, the prominent role of modern biophysical methods of analysis in current bone research was outlined. These methods extend considerably the lower limits of sensitivity in structural and chemical analysis. X-ray diffraction allows an appreciation of molecular structure, while microradiography can provide information regarding the content of mineral in microscopic areas, with a sensitivity far exceeding that of any existing chemical method.

It is the purpose of the present investigation to apply these biophysical analytical methods to human fetal bone, in order to gain new information about mineral distribution and rate of mineral deposition as well as about the ultrastructure of fetal bone and its relation to development.

II. Experimental Materials

All of the material employed in this investigation was obtained from human fetuses, the course of development of which was terminated surgically. Surgical intervention was therapeutic in nature, being based upon considerations of maternal health, and did not reflect the existence of any developmental abnormalities in the fetuses themselves. Fetal samples were supplemented by those from non-viable premature infants and those of full-term, still-born or non-viable infants. In these, the cause of death was never associated with primary skeletal disease nor was there a secondary pathological involvement of the skeleton. In all instances, therefore, the material utilized for this study is felt to be representative of physiologically

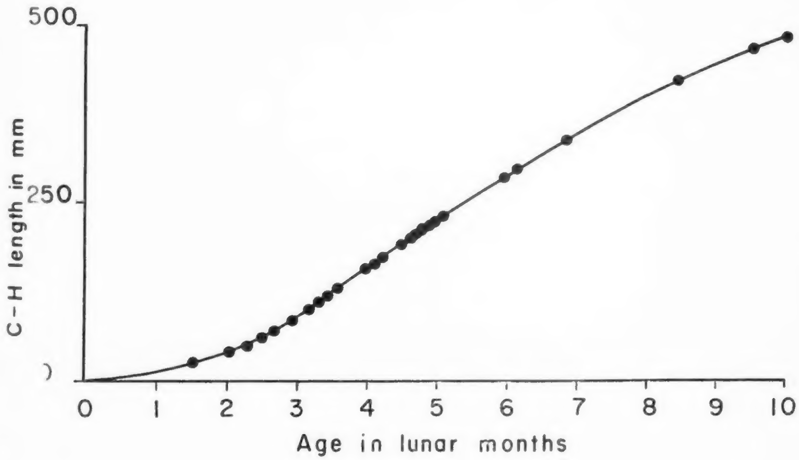

Fig . Age distribution of the material used in the present study plotted from a fetal length-fetal age nomogram (87). Fetal length is expressed in terms of the crown-heel length. Each point represents one specimen.

normal bone development and growth. All samples were fixed in absolute alcohol as soon as possible after recovery.

The total number of individuals examined was 26, the crown-heel length of which ranged between 30 and 500 mm. Their true fetal age was determined by referring the observed crown-heel lengths to statistical nomograms of age-length relationships (87). The numerical distribution of the present material in terms of developmental age is indicated in Figure 1. Reference to this figure shows that sampling of the youngest stages of development is quite representative, the maximum discontinuity between samples not exceeding two weeks of development. Some care was exercised in this connection, since at the outset it seemed likely that the most striking changes or differences in the pattern of mineralization might be expected to occur during the earlier developmental stages. More sizable discontinuities in sampling appear among the older stages. However, it will be seen in the following account that these gaps do not affect the significance of the qualitative or quantitative results, principally because less important changes in the mineralization pattern occur during the latter stages of fetal life.

Fetal femurs were chosen as the experimental object for several reasons. As a representative of a typical long bone, the femur possesses a solid and continuous tubular wall, extending from proximal to distal epiphysis. The "anlage" of this wall appears early in development, during the eighth week of gestation (81), and subsequently undergoes a progressive increase in

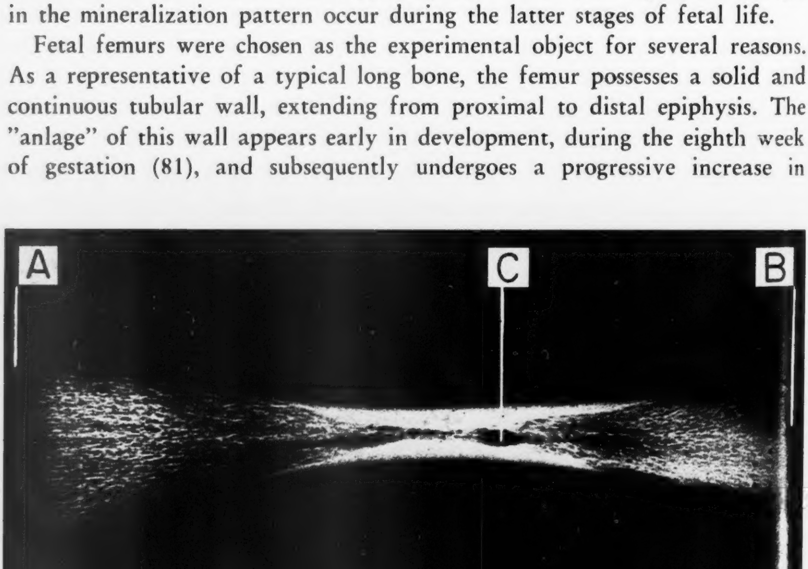

Fig. 2. Fine-focus radiogram of femur from a 30-week-old human fetus. Magnification, × 2. Note the epiphyseal growth zones (A and B) and the projection of the nutrient canal (C). Measurements of intraepiphyseal length were made between points A and B.

thickness and length. The continuity of the bony tube, in both longitudinal and transverse section, suits it ideally for qualitative and quantitative microradiographic study, since those areas undergoing increase in length or thickness can be identified and examined separately of the remaining bony tissue. In addition, since the rate per unit time of increase in the length of the fetal femur is known (95), it is therefore possible to determine the actual age of certain structures within the bone (especially in the epiphyseal growth regions) with a relatively high degree of accuracy. Finally, like all long bones, the femur attains its definitive size and form by a combination of endochondral (epiphyseal) and membranous (periosteal) ossification. It is thus possible in a study of this type to examine each of these processes independently of the other.

The fixed femurs were freed of adherent soft tissues, and were then radiographed with a fine focus x-ray unit (Hilger) to determine the precise intra-epiphyseal length of each bone (Figure 2). One femur from each fetal sample was then embedded in methyl methacrylate. Plastic embedding was carried out by immersing the bones in a 1: 1 mixture of absolute alcohol and methyl methacrylate monomer for 24 hours, followed by two changes of 24 hours each in pure monomer. Following this, the samples were placed in monomer containing 2 per cent benzoyl peroxide as catalyst, which was then polymerized for 24 hours at 40° C. The polymerized methyl methacrylate forms a hard and transparent supporting matrix, which allows the samples to be cut and ground down to thicknesses suitable for microradiographic exposure.

The plastic embedded samples were cut on a circular saw designed to provide thin sections. The primary saw cuts were made so as to yield two sections from each sample: The first, a cross section through the mid-diaphyseal region, including the point of entry of the principal nutrient artery (to be used subsequently as a reference point); the second, a longitudinal section through the distal half of the sample, midway between its dorsal and ventral surface. The freshly sawn sections were approximately 0.5 mm in thickness, but were then carefully ground down on abrasive paper to a final thickness of about 100 microns. As a final step in the hand grinding process, the samples were polished on a plane glass surface lubricated with alcohol.

It should be noted that the ultimate section thickness used in all experiments was optimally suited for x-ray absorption measurements, having been derived from the relationship:

$$t = \frac{1}{u} \qquad [1]$$

where t is optimal thickness in cm for quantitative absorption studies, and μ is the linear absorption coefficient of the substance being investigated, which in the case of bone is approximately 100 at the x-ray wavelength employed here. This experimental thickness is also optimally suited for x-ray diffraction examination of the mineralized structures.

The remaining femur from each fetal sample was then dried in moderate heat to a constant weight. These bones were then either pulverized for x-ray diffraction studies of particle size, or were decalcified in a 34 per cent aqueous solution of disodium, dihydrogen ethylene diamine tetraacetate (EDTA) for studies of the organic matrix.

III. Microradiographic Studies of the Dynamics of Fetal Ossification

A. Introduction

A primary formulation of the theory of quantitative microradiography and the first application of the method to the determination of mass distribution in biological samples was presented by Engström in 1946 (41). Subsequent to that time rapid refinements in the technique and considerable extension of its area of application have provided valuable information regarding the distribution of a variety of substances in extremely small biological samples (42).

The inorganic fraction of bone particularly lends itself to study by this method, because the mass absorption coefficient of the bone mineral is markedly different from that of the organic matrix, as long as relatively short wavelength x-rays are utilized (see below). During the past five years, a number of reports have appeared dealing with the mass distribution of bone mineral under normal and pathological conditions.

In studies of the comparative mineral distribution in bone from a variety of species of mammals, Engström and Amprino (43) showed that primary, or periosteal bone possesses a mineral content 5 to 20 per cent higher than that of the secondary bone which forms the Haversian systems. They also demonstrated that during the process of maturation of new but fully-formed Haversian systems, the lamellae nearest the central canal possess a greater mineral content than the more peripheral lamellae. They also suggested that primary bone probably attains a higher and more stable degree of mineralization more quickly than does secondary bone. This concept was later restated by Amprino (1) in a study of the influence of the organic matrix upon the x-ray absorption values observed for bone mineral.

Utilization of the microradiographic method enabled Owen *et al.* (86) to investigate internal reconstruction in the growing rabbit tibia. Subsequently, Owen (85) did quantitative estimates of the degree of mineralization in various parts of rabbit bone and found strikingly different levels of

calcification in calcified cartilage, in bone adjacent to the latter, and in periosteal bone. Applied to bone pathology, the microradiographic technique has also demonstrated characteristic alterations of the mineral content and distribution in bone in a variety of diseases (33, 34, 35, 36, 37, 39), and has even been of assistance in the characterization of a previously unrecognized bone abnormality (40).

A review of the literature thus emphasizes the fact that microradiographic studies of mineral content and distribution in bone have already provided valuable new information regarding the physiology of mineralized tissues, and offer an extremely useful tool for further investigation and possible elucidation of the many and varied questions associated with bone growth and metabolism which remain unanswered.

This section seeks to provide new information regarding the pattern and rate of mineralization in the fetal femur, expressed in quantitative terms. The technique of quantitation which is used in the present experiments differs from those reported previously by others (2, 85), and shall be described and discussed in detail below.

B. Methods

Absorption of monochromatic x-rays in all matter follows the relationship:

$$I = I_0 \cdot e^{-\mu \cdot t} \qquad [2]$$

where I is the transmitted x-ray intensity, I_0 is the incident x-ray intensity, e is the base of the Naperian logarithm, μ is the linear absorption coefficient, expressed in cm^{-1}, for the absorbing medium, and t is the thickness of the medium in cm.

Instead of the linear absorption coefficient, the mass absorption coefficient $\left(\frac{\mu}{\varrho}\right)$ with the dimension $cm^2 \cdot g^{-1}$ is often used as an alternative expression, in which case the absorption equation is written:

$$I = I_0 \cdot e^{-\frac{\mu}{\varrho} m} \qquad [3]$$

where m is the mass of the specimen in $g \cdot cm^{-2}$

When several absorbing components with the weight fractions m_1, m_2, m_3, etc., are present in the sample, the x-ray absorption is calculated from the equation:

$$I = I_0 \cdot e^{-\left(\frac{\mu_1}{\varrho_1} m_1 + \frac{\mu_2}{\varrho_2} m_2 \ldots\right)} \qquad [4]$$

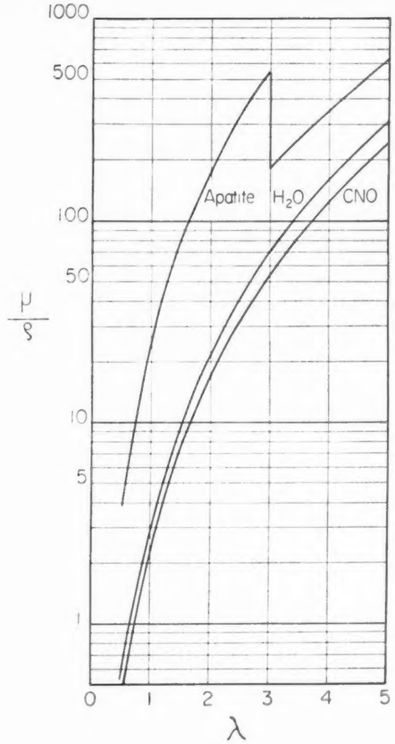

Fig. 3. Mass absorption coefficients for calcium-hydroxy-apatite, $Ca_{10}(PO_4)_6(OH)_2$, for protein in the diagram labelled (CNO), and for water (H_2O), computed from the empirical formulae given by Jönsson (108). The absorption discontinuity in the apatite curve is due to the K-absorption edge of calcium at 3.05 Å.

In order to determine the x-ray wavelength most suitable for microradiography of thin bone specimens, the mass absorption coefficients for calcium-hydroxy-apatite, protein and water were calculated from the empirical formulae given in the literature (108). These calculated values are plotted on the graph shown in Figure 3 for wavelengths up to 5 Å. This graph indicates that between 0.5 and 3 Å the mass absorption coefficient of apatite is roughly ten times that of water or protein. In this wavelength range, therefore the major part of the x-ray absorption in a bone sample is caused by the mineral compartment, and the microradiographic images formed by radiation of this wavelength will thus demonstrate the distribution of mineral elements in the sample.

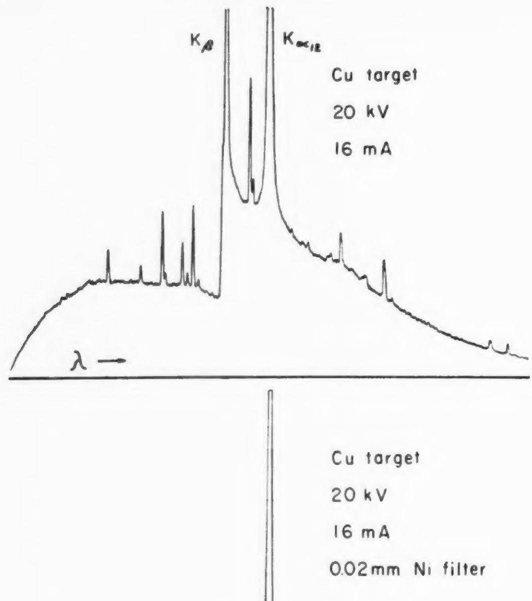

Fig. 4. Upper figure: Geiger counter spectrometric registration of the total radiation at 20 kV from a copper target tube.
Lower figure: Monocromatizing influence of filtration through a 20 micron nickel filter on the copper line radiation.

The characteristic line radiation of copper (Cu Kα line radiation = 1.54 Å.) is from a technical point of view admirably suited for microradiographic studies of bone mineral. An x-ray unit of high stability (Philips model PW1010), equipped with a copper target, was employed in this phase of the investigation, and was operated at 20 kV and 16 mA. The resultant "white" or broad spectrum radiation was then filtered through a 20 micron-thick nickel filter, the effect of which is illustrated in Figure 4. It is estimated that under these conditions, more than 80 per cent of the radiation which passed through the nickel filter lay in the wavelength range 1.5 to 1.6 Å, the major part being derived from Cu Kα line radiation. Thus, for the purposes of this experiment, the radiation could be considered to

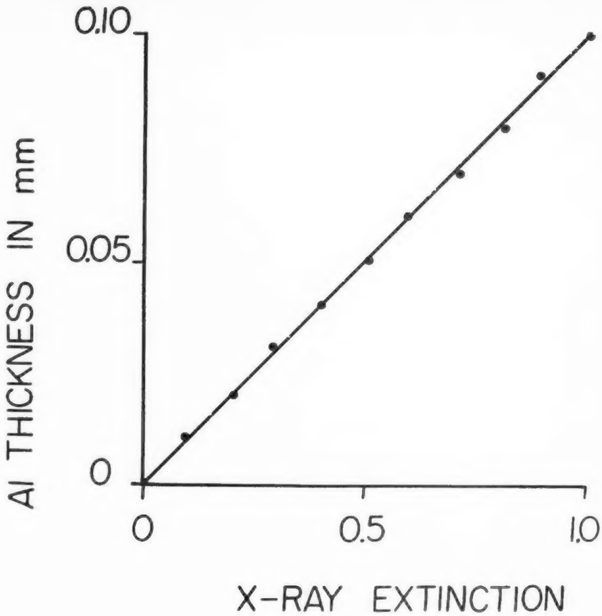

Fig. 5. Relationship between progressive increase in mass of an aluminium stepwedge absorber and the x-ray extinction of the radiation used in this study. The straight line relationship indicates that the radiation is sufficiently monochromatic to obey the law for absorption of monochromatic x-rays (Formula 2).

be monochromatic. It was found (Figure 5) that the absorption of this radiation in stepwedges made up of carefully selected thin and plane parallel aluminium foils followed the theoretically calculated direct relationship between mass and the extinction of monochromatic x-rays.

All of the microradiograms made in the course of this part of the investigation were recorded on Eastman Kodak Spectroscopic Plate No. GH 649, with emulsion numbers 499 and 502. Up to a photographic density of 0.7–0.8 these emulsions were found to possess a linear density response to the radiation employed (Figure 6).

During exposure, the plastic embedded sections were kept in close contact with the recording emulsion. The target to film-sample distance was maintained at 30 cm in order to provide high resolution in the images, and at the same time to provide as even a field of x-ray illumination as possible. Structures in the microradiograms with diameters down to 1 micron could be differentiated readily under these conditions of preparation.

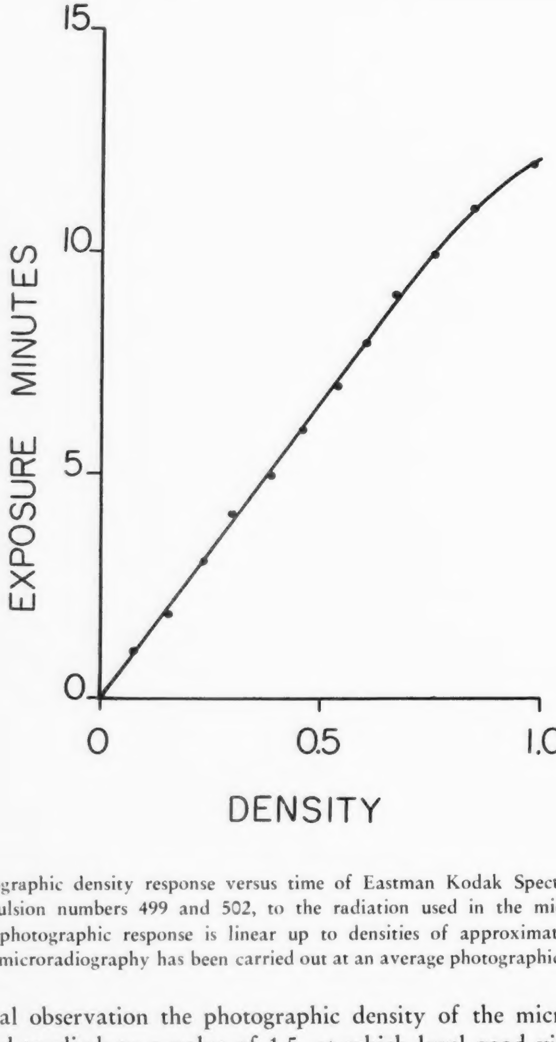

Fig. 6. Photographic density response versus time of Eastman Kodak Spectroscopic Plates No. 649, emulsion numbers 499 and 502, to the radiation used in the microradiographic studies. The photographic response is linear up to densities of approximately 0.8 to 0.9. Quantitative microradiography has been carried out at an average photographic density of 0.6.

For visual observation the photographic density of the microradiograms was allowed to climb to a value of 1.5, at which level good visual contrast is obtained. For densitometric determinations, however, the density was kept within the range in which photographic response is linearly related to x-ray intensity, that is, in the range of 0.5 to 0.7. The exposed microradiograms were then developed for 4 minutes at 20° C in undiluted Kodak D-19b developer, and thereafter processed according to routine photographic procedures.

Thus, by utilizing "monochromatic" radiation, and by maintaining photographic density within the limits for linear response to the x-rays used, it is possible to arrive at absolute values for the degree of x-ray absorption without the use of any artificial reference system. One need only substitute the densitometrically obtained light transmission values for the quantities I and I_0 in the relationship noted above as formula 2.

Microphotometric evaluation of the microradiograms was performed with a Zeiss "Schnellphotometer". This instrument was equipped with optics which minimized the possibility of scattered or otherwise extraneous light being registered by the photocell. For determination of the x-ray absorption of any given sample, three densitometric readings had to be made. These were first, on an area of unexposed emulsion which had been protected by a lead stop during exposure; second, on a point chosen within the sample itself; and third, on a portion of the emulsion exposed to the direct x-ray beam. The latter two readings could be made very close to one another, since readings from the sample were always made near a free edge, and were thus adjacent to the unprotected emulsion. This arrangement tended to minimize any errors which might have otherwise been introduced by variations in the intensity of the x-ray beam or in the photographic emulsion itself. In order to increase the accuracy of the readings from the mechanical point of view, the largest photometric response, i.e., that to the unexposed emulsion, was arbitrarily adjusted by varying the field size so as to give an actual reading on the instrument of approximately 50 scaleunits (the scale being readable to deflections of one-half unit). When the illumination through unexposed emulsion had a value of 50, the field of observation, at a magnification of 33 diameters, was approximately 400 square microns in area.

If the transmitted light intensities recorded under these conditions are called P_0, P_s and P_d, for the values given by unexposed emulsion, the sample, and the area exposed by the direct beam respectively, the value of I_0 in the x-ray absorption relationship (formula 2) may then be substituted by the expression:

$$I_0 = k \log_{10} \frac{P_0}{P_d} \qquad [5]$$

while the value of I in the same formula may be expressed as:

$$I = k \log_{10} \frac{P_0}{P_s} \qquad [6]$$

in which k is a constant.

From these measurements of light transmission it is thus possible to solve the value of $\mu\ t$, the product of the linear absorption coefficient and the sample thickness, in the x-ray absorption equation (formula 2).

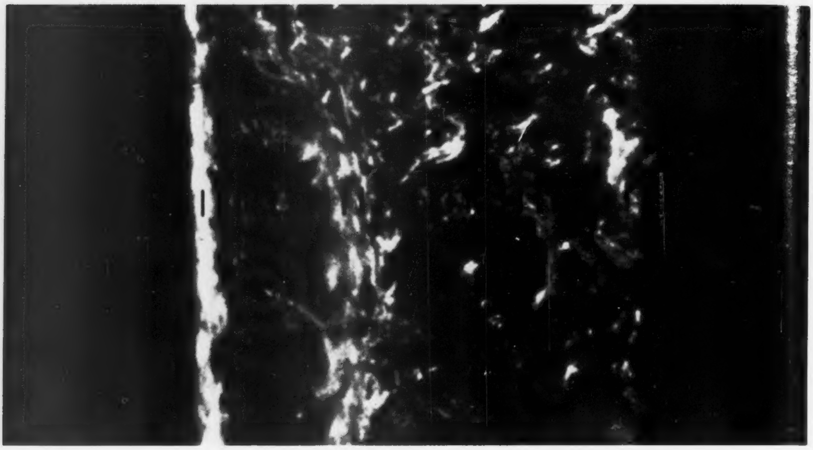

Fig. 7. Cut edge of a plastic-embedded section as viewed in the profile microscope employed for thickness determinations. Every scale unit corresponds to an interval of 4.3 microns. Magnification, x 600.

However, in order to arrive at a final value for the linear absorption coefficient itself, it is first necessary to determine the sample thickness. In this study the following method was employed for determination of sample thickness. The samples were cut with a microdissection knife so that all of the structures to be examined came to lie at the free cut edge. The cut samples were set on edge so that the area of interest lay free, and its thickness was then measured by micrometry in a profile microscope employing reflected light. This method is illustrated in Figure 7. Comparison of the thickness of cut edges with those which had simply been broken revealed that the process of cutting had no effect upon the thickness of the samples. The accuracy of the thickness measurements, which were carried out at a magnification of 160 diameters, was estimated to be in the order of $\pm$ 2 microns. Never in any of the measurements were differences in thickness observed which exceeded 5 microns per 250 microns of linear surface. Even this difference was a gradual one and did not cause any sudden change in thickness within a limited area.

Occasionally during the course of this investigation, microradiographic and thickness studies were made of homogenous structures, in which case no morphological features were apparent enough to serve as landmarks when comparing the thickness measurements with specific points in the micro-radiographic image. In these circumstances a method was adopted whereby thickness measurements were made at equidistant points along the edge of the

structure under investigation, whereafter these points were then measured out on the companion microradiogram. Densitometry was then carried out at these points, the subsequent calculation being made on the basis of the observed thickness for them.

Thus having determined the values of I and I_0, as well as the actual thickness of the sample, the absolute value of the linear absorption coefficient (μ) can be derived. Since the mass absorption coefficient $\left(\frac{\mu}{\rho}\right)$ is constant, provided that no qualitative changes in the composition of the bone salt occur, any changes in the value of the linear absorption coefficient (μ) reflect changes in the sample density (ρ), i.e., the degree of mineralization. Calculation of the linear absorption coefficient from the observed densitometric and thickness measurements has been greatly facilitated by the use of a slide-rule device especially designed for this purpose by Lundberg and Henke (77).

C. Results

1. Visual Observations

The first bone which appears in the human fetal femur forms the tubular primary periosteal collar surrounding the diaphyseal portion of the embryonic cartilage model. It is first seen in embryos whose crown-rump lengths range from 24 to 35 mm (81), their average length corresponding to a fetal age of approximately 8 weeks (87). In the present study, the youngest femur which showed evidence of primary ossification was obtained from a 9.5-week-old embryo, so that the actual mineral deposits present were those which for the most part had been formed during the preceding 10 days. A microradiographic image of the transverse section taken through this specimen is presented in Figure 8. The reader should note in the interpretation of this and of subsequent microradiograms that, as in ordinary radiographic illustrations, those areas exhibiting the greatest x-ray absorption (highest mineral content) appear white, while areas of lesser absorption appear in various tones, ranging from pale gray to black.

Reference to Figure 8 allows the following observations to be made concerning the morphological patterns of mineralization at this early developmental stage. It may be seen that the newly-formed primary periosteal collar does not completely encircle the cartilage model. Many discontinuities, in addition to the one which allows passage of the nutrient vessels, appear along its circumference. Moreover, the collar appears to be made up of two types of bone, the inner one of which appears at the junction of the

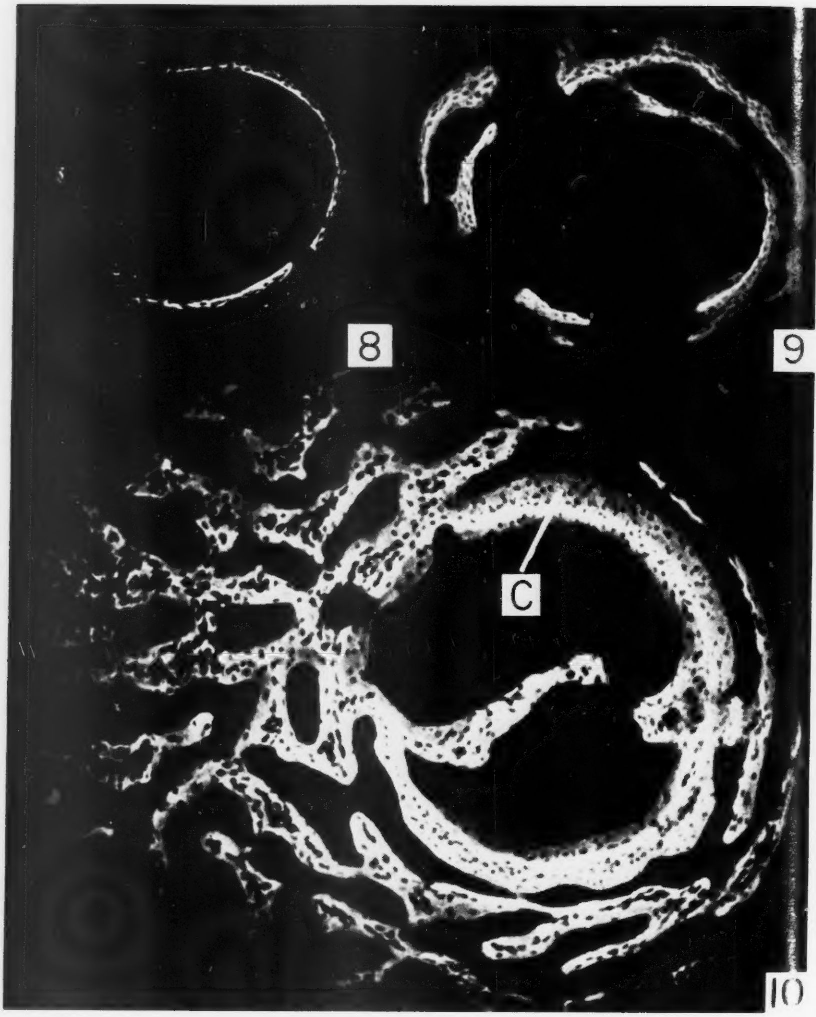

Fig. 8, 9, and 10. Microradiograms illustrating progressive stages in the formation of the primary periosteal collar (C) and periosteal bone in mid-diaphyseal cross sections of the femur from fetuses 9.5 weeks (Fig. 8), 10,5 weeks (Fig. 9), and 15 weeks of age (Fig. 10). Magnification in all figures, x 85.

At 9.5 weeks (Fig. 8), the primary periosteal collar exhibits two types of structure, an inner, acellular and highly mineralized zone, and an outer cellular layer possessing a lower level of mineralization.

At 10.5 weeks (Fig. 9), the inner zone of the collar is clearly apparent, by virtue of its high level of mineralization. The outer layer of the collar has increased in thickness by apposition

collar with the primitive marrow cavity. It is a rather homogenous, solid and well mineralized layer, and judging from the relatively few osteocytic lacunae which are present, it is mainly acellular. Immediately outside this layer, however, a somewhat more cellular or lacunar structure is seen, and the degree of mineralization of the bone in this region seems to be slightly less than that of the innermost, acellular layer.

Figures 9, 10 and 11, respectively, illustrate cross sections taken from the periosteal bone collars at 10.5, 15 and 24 weeks of fetal development. Examination of these figures reveals that the primary periosteal bone collar remains intact, and in fact becomes continuous about the circumference of the marrow cavity (excepting in the region of the nutrient foramen). It remains closely adjacent to the marrow cavity, and rapidly increases in thickness. The original innermost layer attains a level of mineralization higher than that of the rest of collar. Using this hypercalcified layer as a structural landmark, it is seen that the collar maintains its structural integrity throughout the greatest portion of the intrauterine life of the bone. Indeed, portions of it can even be recognized at the time of birth (Figure 12).

The figures also indicate that new bone, possessing a relatively low x-ray absorption, is formed progressively by apposition at the endosteal surface of the collar. Progressive appositional growth of new bone also occurs at the periosteal surface of the collar, although at a more rapid rate.

Periosteal bone formation occurs first in direct contact with the hypercalcified layer described above (Figures 9 and 10), but later manifests itself in a series of concentric, discontinuous, and rather evenly spaced layers of bone (Figure 11). Periosteal bone differs structurally from that of the primary collar. At its first appearance, each layer is made up of a rather cellular, lacunar type of bone, the mineral content of which is quite high (Figure 10). During later development, each of these highly mineralized and cellular

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of new, cellular bone of relatively low mineralization. On the endosteal surface of the collar may be seen some evidence of beginning endosteal bone formation, this bone possessing a low mineralization. Outside of the collar appear several layers of periosteal bone, which are seen to be very cellular.

By 15 weeks (Fig. 10), the primary periosteal collar (C) has become considerably increased in thickness by the addition of further layers of cellular bone to its circumference. This bone is seen to have attained a reasonably high level of mineralization at this time (compare to Fig. 9). The innermost zone of the collar is easily recognized by its lack of cellular structure and its very high mineral content. On its inner surface, a layer of endosteal bone of low mineralization is seen. The layers of periosteal bone have increased in number. Their cellular nature is apparent, and their degree of mineralization varies, being relatively high toward the center of the bone, less so at its periphery.

Fig. 11. Microradiogram of the mid-diaphyseal cross section of a femur from a 24-week-old fetus. Magnification, x 40.

The primary periosteal collar (C), with its hypercalcified zone, as well as the endosteal bone on its inner surface, is easily identified. The number of layers of periosteal bone has been greatly increased, and the original cellular bone of each layer has become enveloped by bone of a less cellular composition which possesses a lower level of mineralization. The level of mineralization of this bone, as well as that of the central cores, is seen to decrease from the center of the bone to its periphery.

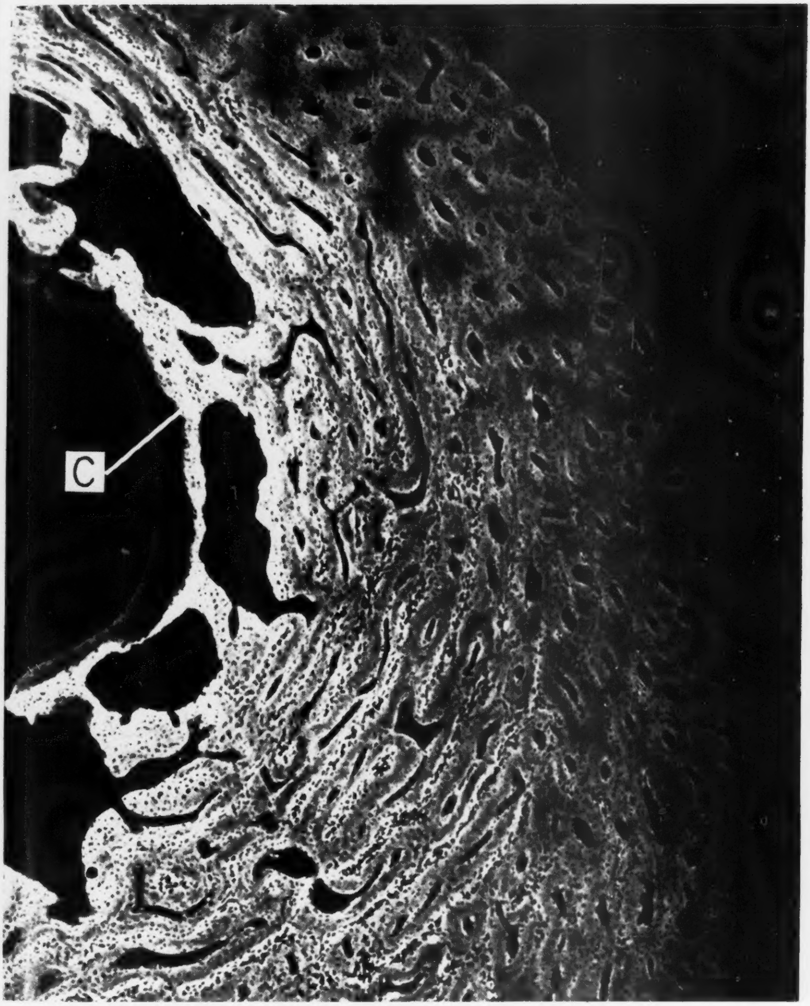

Fig. 12. Microradiogram of a sector of the mid-diaphyseal cross section of a femur from a 40-week-old fetus. Magnification, x 50.

The primary periosteal collar (C), and its inner hypermineralized zone, are still evident, even at the time of birth. Adjacent to the collar are seen layers of periosteal bone, each of which is made up of a central hypercalcified and cellular core, surrounded by lamellae of less calcified and less cellular bone. At the periphery of the section and extending for some distance centrally, the periosteal bone layers are being replaced by young Haversian systems. Note the endosteal bone on the inner surface of the primary periosteal collar, which is seen to possess a strikingly low mineral content.

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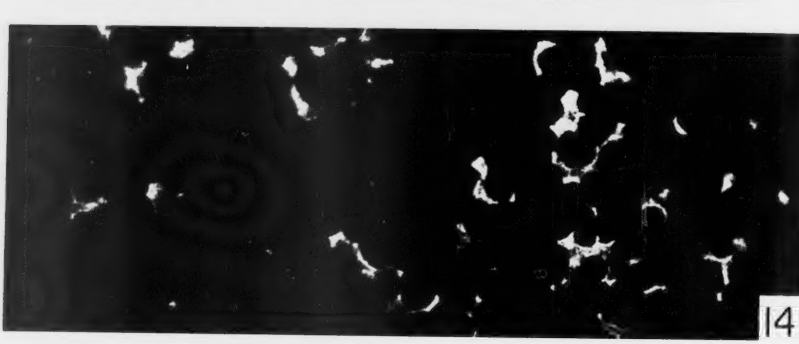

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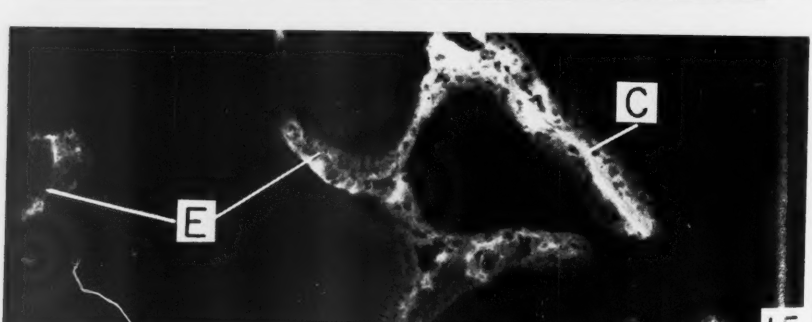

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Fig. 13, 14, and 15. Microradiograms of sectors of cross section through the epiphyseal zone of provisional cartilage calcification and through the adjacent metaphyseal zone of endochondral ossification. Femur from a 17-week-old fetus. Magnification in all figures, x 20. Fig. 13 is a section taken at the level of the zone of cartilage hypertrophy. The calcified cartilage between the columns of hypertrophied cartilage cells appears as a system of irregular, interconnecting membranes.

At the level of cartilage cell degeneration (Fig. 14), the calcified cartilage exhibits an increased x-ray absorption, but at the same time a considerable decrease in total volume

structures acts as a central core about which are applied new layers of less cellular and less mineralized bone (Figure 11).

In sections taken from the older individuals, the concentric periosteal bone layers are seen to be less well interspaced. The original spacing appears to have been obliterated by the formation of new peripheral coatings of bone about their hypermineralized cores (compare Figures 11 and 12). Comparison of the relative number of periosteal bone layers in the cross sections in Figures 9 through 12 shows that their formation occurs relatively rapidly during fetal development. Within each of the more centrally located layers of bone, the level of mineralization of the cellular core remains greater than that of the bone surrounding it, but the latter nonetheless possesses an even and rather high degree of mineralization. It is not until one passes from the center of the cross section to its very periphery, that the bone layers about each cellular core exhibit a decreased mineral content. It appears, then, that not only are the layers of periosteal bone formed rapidly, but they also quickly attain a relatively high mineral content.

In the youngest periosteal bone layers, i.e., those nearest to the periosteum, it is possible to visualize the local progress of the mineralization process. Here, it can be seen (as in Figure 11) that the peripheral layers about each core exhibit a patchy appearance which is indicative of local variations in their mineral content. Such an appearance suggests that during growth there exist particular or specific points in the new bone which are favored for the initiation of mineralization.

The central cores of each periosteal bone layer retain a high degree of mineralization throughout fetal life (Figures 11 and 12). Shortly before term, the cores, along with their surrounding layers of less mineralized bone, begin to be replaced by newly-formed Haversian systems, whose mineral content is relatively low. Thus, the periosteal bone layers are progressively broken up, and come to lie in interstitial positions among the new Haversian systems. But they may still be identified in microradiograms by the presence of their hypercalcified cores (Figure 12).

The structure and pattern of mineralization in the primitive Haversian systems may be appreciated in Figure 12. Adjacent to their central canal they exhibit the characteristic zone of high mineralization which has already been described by others (2).

(compare to Figure 13). The calcified cartilage remnants appear as irregular, angular, and coarse fragments.

In the metaphysis (Fig. 15), layers of endochondral bone possessing a relatively low degree of mineralization (E) have been laid down about the highly calcified cartilage remnants. All endochondral bone is separated from bone arising in the periosteum by the primary periosteal collar (C).

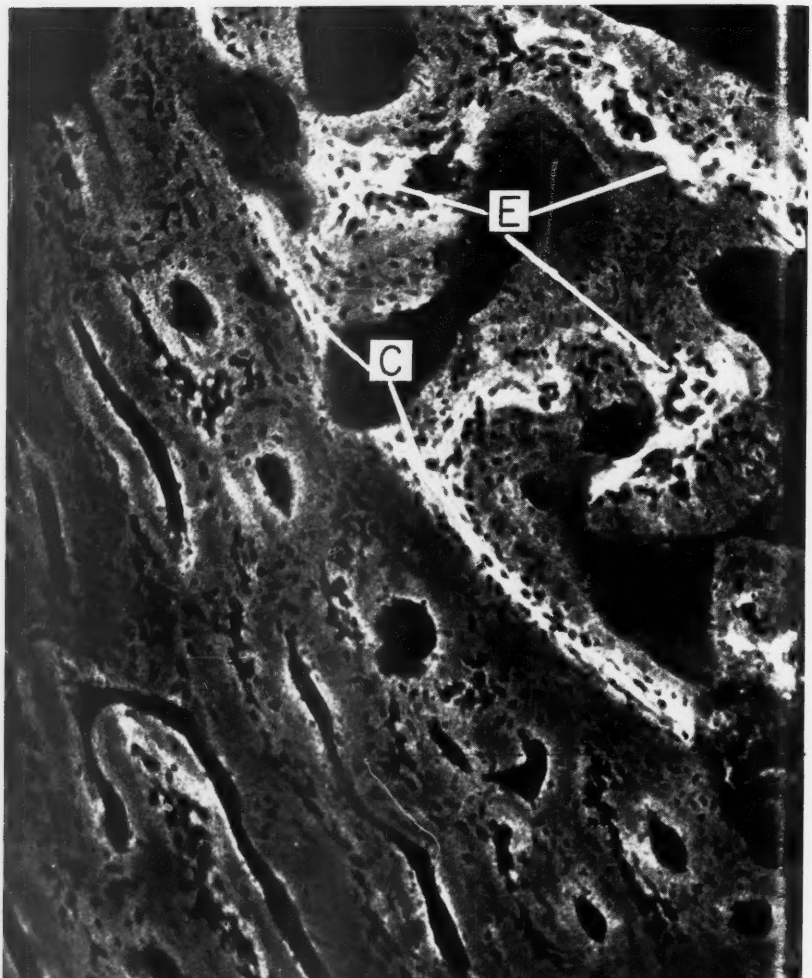


Fig. 16. Microradiogram of a sector of a cross section through the metaphyseal region in a femur from a 30-week-old fetus. Magnification, x 200.
The primary periosteal collar (C) separates endochondral bone (E) from periosteal bone. The hypercalcified inner zone of the collar, as well as the hypercalcified cartilage remnants in endochondral bone (E) stand out clearly. Periosteal bone layers partially replaced by Haversian systems, the central areas of which show a higher degree of mineralization than do their more peripheral lamellae. At the top center of the figure is an area of endosteal bone which exhibits a typically low content of mineral.

Endochondral bone formation and mineralization was examined in a series of semi-serial cross sections from the femur of a 17-week-old fetus. The sections were taken at intervals of approximately 2 mm, beginning in the zone of hypertrophied and calcified cartilage in the epiphysis, and extending down into the metaphysis. Three such sections are illustrated in Figures 13 to 15.

In the zone of provisional calcification (Figure 13), the tiny calcified spicules between the hypertrophied cartilage cells give the appearance of being delicate membranes. The remarkable depth of field provided by the microradiographic method gives them a somewhat three-dimensional quality in the figure. As the section level approaches the metaphysis (Figure 14), the membranous appearance of the calcified tissue is lost, and only a few coarse, angular, and irregular remnants are seen. At a slightly lower level (Figure 15) these cartilagenous remnants are seen to form cores around which bone is applied. The bone thus formed, however, has a much lower degree of mineralization than does the calcified cartilage core itself.

Endochondrally-formed bone which becomes incorporated into the metaphyseal wall of the bone during subsequent growth may be identified readily at later stages, since the cores of calcified cartilage always retain a mineral content higher than that of the surrounding bone. This fact has been of considerable value in studies of the internal reconstruction of bone, in which it is necessary to distinguish between periosteal and endochondral bone (66).

During intrauterine development of the human femur, the part played by endochondral bone in the formation of the diaphyseal bone collars is probably very minor, being limited to the incorporation of small bits of endochondral, cartilage-containing bone into the endosteal face of the metaphysis (Figure 16). This bone, however, is always found inside of the primary periosteal bone collar, and so can easily be differentiated from periosteally-formed bone.

Visual examination of microradiograms of developing fetal bone, then, permits the distinction of three types of mineralized tissues. Grouped according to their mineral content, these are: 1) Newly-formed bone possessing a rather low and inhomogeneous degree of mineralization; 2) older bone, which constitutes by far the greatest share of the tissue, and which exhibits a high and homogeneous level of mineralization; and 3) hypermineralized bone and calcified cartilage remnants, which possess an extremely high degree of mineralization, and which appear to act as centers about which new bone is laid down. Visual examination suggests that there is no significant difference in the levels of mineralization of hypermineralized bone and of calcified cartilage remnants.

From the foregoing presentation, it is evident that none of the fetal bone

is, strictly speaking, homogeneous, but each of the three types occurs in close structural association with the others. This fact creates some difficulty in chosing a particular area for use in quantitative densitometric studies, since the structure selected should possess a reasonable degree of homogeneity. The mechanical limitations of the photometer described previously make necessary the use of a field of view approximating 400 μ^2 in area. Obviously then, whatever structure is chosen for study must be large enough to fill this field completely. Moreover, in order to permit comparison of the same area in various samples, the structure of choice must also be one which can be identified at all stages of fetal development.

Consideration of these factors led to the choice of the primary periosteal bone collar (Figure 10, 11 and 12, C), adjacent to the primitive marrow cavity, as the best possible experimental object for quantitative study. This structure is reasonably homogeneous, excepting for the presence of its hypercalcified ring, whose influence on the measurement will be discussed in the following section. The collar is large enough to meet the requirements of the photometric method, and it can be traced readily from its first appearance early in the third fetal month right up to the time of birth.

2. Quantitative Observations

a. *Mature Fetal Bone:* The visual observations cited in the previous section have indicated that bone eventually attains two distinctly different levels of mineralization in the mature fetus. Respectively, these are the large masses of periosteal bone which attain a uniform and high level of mineralization, and the hypercalcified bone which is found at the center of each individual layer of periosteal bone.

In order to express the degree of mineralization of the first of these types of bone in absolute terms, densitometry was performed in the primary periosteal collar. These measurements were carried out on samples from older fetuses, in which the collar had attained sufficient thickness to avoid inclusion of its hypercalcified innermost component (Figure 11).

It has been pointed out that visual comparison failed to reveal any significant difference in the degree of mineralization of the hypermineralized bone and the calcified cartilage remnants. This fact, coupled with the difficulty of finding areas of hypermineralized bone which completely filled the photometer field, led to the use of particularly large and solid calcified cartilage remnants as the object for examination of mineralization levels. The absolute values attained in this way are considered to be representative also for hypermineralized bone.

Table I presents the absolute values for the degree of mineralization, expressed as the mean linear absorption coefficient, in periosteal bone and hypercalcified bone (calcified cartilage), together with similar figures obtained from adult bone. The table shows, that for the most part, fetal periosteal bone, possesses a degree of mineralization somewhat lower (approximately 16 per cent) than adult bone. On the other hand, the hypermineralized bone and calcified cartilage appear to attain a mineralization level from 8 to 10 per cent higher than that of the adult.

TABLE I.
Characteristic Levels of Mineralization in Calcified Tissues from Fetal and Adult Specimens

Sample	Number of observations	Mean linear absorption coefficient	Standard deviation
Fetal bone with an even degree of mineralization	20	82.3	2.4
Fetal hypercalcified bone and/or calcified cartilage	10	100.3	1.7
Adult bone	20	95.1	5.2

b. *Developing Fetal Bone:* The primary periosteal collar is the first bone to be laid down in the human femur. This structure can be followed in an intact form throughout almost all of the fetal period, and thus presents itself as an area whose actual age can be estimated with some accuracy in different samples. It is therefore ideally suited as the test object for determining the rate of mineralization during development.

Mid-diaphysal cross sections from the femurs of individuals representing different stages of fetal growth were cut into five parts, in such a way that a total of eight evenly-spaced points about the circumference of the ring of primary periosteal bone were available at the cut borders for examination. The thickness at each point was measured according to the method already described. The cut samples were then microradiogrammed and their x-ray images measured densitometrically. The highest absorption value obtained at each point was utilized in calculation of the linear absorption coefficient.

Table II presents the results of this study, and indicates the degree of mineralization in seven different fetal stages of development. The level of mineralization is expressed as the mean linear absorption coefficient computed from the eight individual observations made on each sample.

TABLE II.
Changes in the Mineralization of Femoral Diaphyseal Cross Sections during Fetal Growth

Crown-rump length of fetus (mm)	Number of observations	Mean linear absorption coefficient	Standard deviation	Standard error
45	8	68.8	6.3	2.2
61	8	87.8	6.6	2.3
90	8	89.7	4.9	1.7
100	8	91.5	3.9	1.4
125	8	94.4	3.8	1.3
200	8	89.7	3.3	1.2
350	8	94.7	2.7	1.0

These data illustrate the striking fact that, even in the youngest specimen, bone of the primary periosteal collar has attained a rather high degree of mineralization. Values of individual observations obtained at this age, however, are rather variable, as is seen by the magnitude of the standard deviation. As the age of the specimen increases, this variability becomes considerably less marked.

The rapidity with which this structure mineralized during development can best be appreciated when the values presented in Table II are plotted graphically against fetal age. Such a representation is provided in Figure 17, in which the arbitrary zero point of mineralization has been set at the fetal age when mineral deposits first appear in the collar, i.e., at 8 weeks. It is evident that the increase in mineral content is very rapid during the first three weeks after the initial appearance of the bone, after which time the progress of mineralization is much retarded. The degree of mineralization of the periosteal bone collar after 5 to 6 weeks of growth is maintained at an almost constant level during the remainder of fetal life.

The final level of fetal mineralization, as determined by this series of measurements, appears somewhat higher than that obtained from mature fetal bone (Table I). This difference results from the fact that the measurements include the highly mineralized inner zone of the primary collar. An assessment of the influence of the latter structure upon the mineralization values was therefore made by studying the epiphyseal extremities of the periosteal bone collar in longitudinal sections of femurs. The hypermineralized ring does not extend into these regions. Moreover, examination of the epiphyseal ends of the bone collar, which grow rapidly in length, allows an appreciation of the earliest stages of mineralization. It should also indicate by

inference whether the hypermineralized ring of bone seen in the diaphysis might have any direct biological influence upon the rate of mineralization in that region.

Longitudinal sections from six femoral specimens, ranging from 12 to 21 weeks of fetal age, were examined. The point at which mineral deposits first appeared at the epiphyseal end of the periosteal collar was noted, following which thickness measurements and densitometry were performed at successive intervals of 250 microns extending towards the diaphyseal portion of the bone.

Figure 18 illustrates a longitudinal section typical of the material utilized in this phase of the investigation, that is, a section from the distal half of a femur removed from a 15-week-old fetus. The funnel-shaped primary periosteal collar in this section is seen to enclose the cartilagenous zone of provisional calcification at the epiphysis, and, in fact, extends for a considerable distance beyond the calcified cartilage. The overall structure of the periosteal bone collar in longitudinal section is regular and homogenous in the epiphyseal and metaphyseal regions, but as it extends into the diaphyseal zone it becomes more irregular in appearance. This fact probably reflects the combined activities of vascular invasion and erosion of the diaphyseal wall.

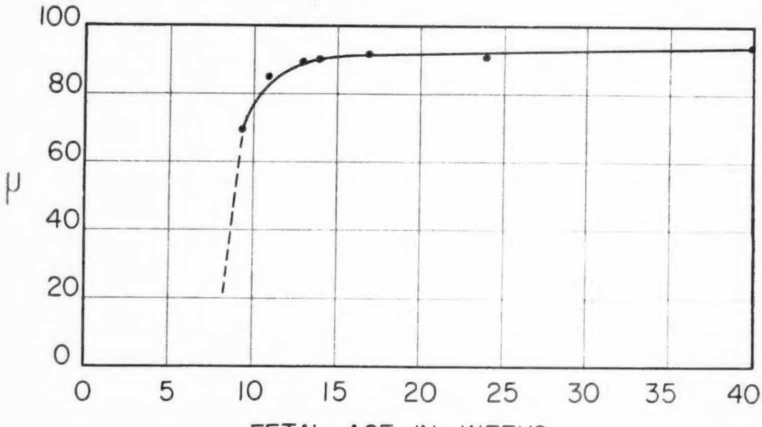


Fig 17. Mineralization of the primary periosteal collar as measured on cross sections from the mid-diaphyseal part of the femur. Values for the linear absorption coefficient for each sample (Table II) are plotted against fetal age. The rapidity with which a high and nearly constant level of mineralization is attained is clearly demonstrated.

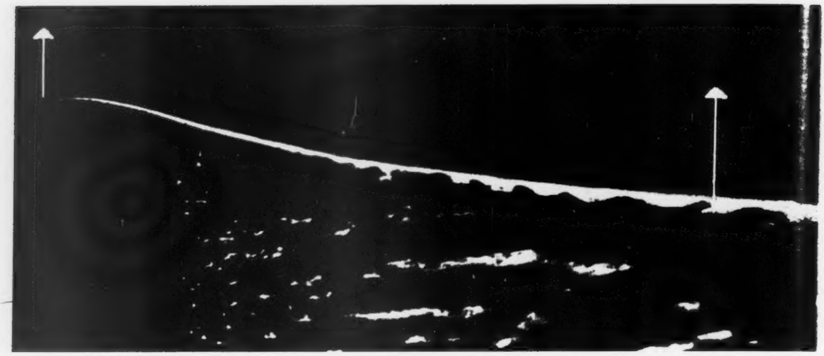


Fig. 18. Low power microradiogram of the distal extremity of the primary periosteal collar viewed in a longitudinal section of a femur from a 15-week-old fetus. The distal epiphysis lies to the left. The arrows mark the limits of the area examined by quantitative microradiography to determine the relationship between epiphyseal bone growth, bone age, and degree of mineralization (see text).

Table III lists the average and maximum linear absorption coefficients obtained from observations made on corresponding points 250 microns apart in the six femoral samples, beginning at the terminal epiphyseal end of the periosteal bone collar, and extending toward the diaphyseal zone. The high standard deviations associated with some of the observations, as well as the fact that the final value for fully mineralized bone in the diaphysis is somewhat lower than that found in a previous series (Table I), undoubtedly results from irregularities in anatomical structure in the metaphyseal regions, rather than from true variations in mineral content. Vascular erosion, for example, causes the bone to become more porous, so that the particular area being examined is not solid throughout its thickness (approximately 100 microns). Thus, the densitometric readings are artificially decreased, and the particular values obtained are not truly indicative of the state of mineralization.

It has been shown previously (95) that there is a direct relationship between the intra-epiphyseal length of the femur and the overall length of the fetus. A plot of the corresponding values taken from the material used in this study has confirmed this relationship. If it were possible to determine the individual contributions of proximal and distal femoral epiphyses to longitudinal growth, either as a ratio or in absolute terms, it would then be feasible to calculate the time required for any given increment in length

to occur at the distal end of the bone. Possession of this value would ultimately allow the determination of the rate of mineralization of the primary periosteal bone collar in the epiphyseal zone.

In 1915, Digby (31) described a method whereby the original mid-point of the femur could be determined by the point of entry of the main nutrient artery into the marrow cavity. With this point as a base, subsequent growth in length at either epipsysis could be measured with considerable accuracy.

Re-examination of the survey radiograms of the material used here, which were originally made to determine intraepiphyseal length, indicated that, of the particular samples utilized in the study of longitudinal growth and mineralization, several exhibited sharply defined nutrient foramina. Measurements from this point revealed that the distal epiphyses were responsible for approximately 55 per cent of longitudinal growth during the twelfth to twenty-first fetal weeks. From this, it was further estimated that the time required for a one mm length increment at the distal end of the bone was of the order of one week.

TABLE III.

Levels of Mineralization in Periosteal Bone of the Fetal Femur at Various Stages of Longitudinal Growth

Distance from epiphyseal tip (mm)	Number of observations	Mean linear absorption coefficient	Highest value	Standard deviation	Standard error
0.25	(No measurement possible)				
0.50	6	22.3	27	3.1	1.3
0.75	6	38.0	45	7.1	2.9
1.00	6	44.8	49	7.8	3.2
1.25	6	48.2	56	7.1	2.9
1.50	6	55.5	68	12.9	5.3
1.75	6	59.8	66	6.7	2.7
2.00	6	59.3	69	6.8	2.8
2.25	6	65.3	79	11.0	4.5
2.50	5	72.0	80	5.6	2.5
2.75	6	71.3	80	5.4	2.2
3.00	5	75.0	85	10.7	4.4
3.25	6	72.8	86	10.0	4.1
3.50	6	73.8	84	6.8	2.8
3.75	6	72.2	84	10.5	4.8
4.00	6	75.5	88	10.2	4.2
4.25	6	78.0	85	6.4	2.6
4.50	5	78.0	83	5.2	2.3
4.75	5	78.8	85	5.1	2.3

By plotting the values shown in Table III for the distal part of the primary periosteal collar against time (Figure 19), one is thus provided with yet another measure of the rate of mineral deposition. This curve has the same characteristics as that constructed from data obtained by study of mid-diaphyseal cross sections (Figure 17), although the final level of mineralization is somewhat lower. The initial, rapid period of mineralization observed previously as lasting for about 2.5 to 3 weeks is also demonstrated by the data presented in Figure 19. As in the previous series, however, the rate of mineralization levels off during subsequent growth.

The pattern of mineralization of the primary periosteal collar has thus been found, in separate observations of two different regions, to be strikingly similar. During the first three weeks of its existence, it mineralizes extremely rapidly. After that time, additional increments in mineral content occur less quickly, an almost constant level having been obtained by the time five weeks have passed. The innermost hypercalcified portion of the periosteal collar apparently plays no role in determining the rate of mineralization of the surrounding bone.

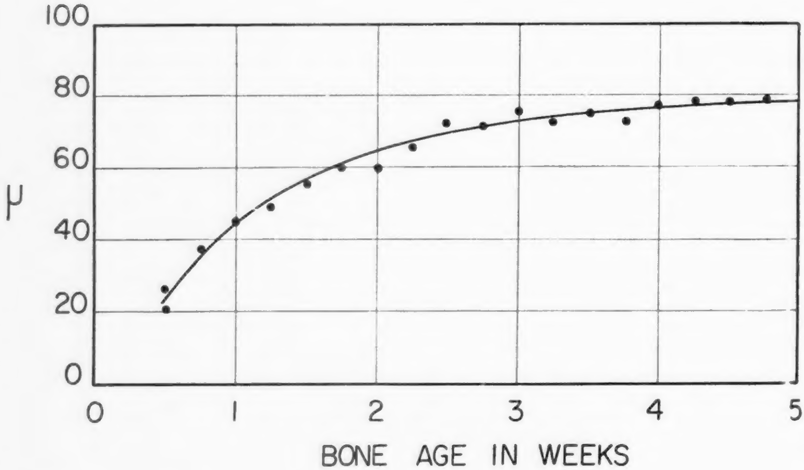


Fig. 19. Mineralization in the distal epiphyseal end of the primary periosteal collar. Values of the linear absorption coefficient are taken from Table III, and are plotted against bone age as determined by the growth rate of the distal epiphysis (see text). During the period of most rapid increase in mineral content, the values shown here are in good agreement with those plotted in Fig. 17.

D. Discussion

The principal advantage of the method used in this phase of the investigation is that it permits a direct calculation of *absolute* values for the linear absorption coefficient of bone. Unlike previous quantitative studies, therefore, an artificial reference system and, with it, associated additional errors, may be omitted. Moreover, errors arising from variations in the intensity of the x-ray beam or in the sensitivity of the photographic emulsion have been minimized by making the necessary densitometric measurements upon very closely adjacent regions on the microradiogram.

The fact that the photographic densities must be kept at relatively low values in this technique may conceivably constitute its chief disadvantage. At the density levels employed routinely, ranging from 0.5 to 0.7, the photographic contrast is markedly reduced, this function of the emulsion in microradiography being optimal at consderably higher photographic densities. Reduction in contrast might therefore be expected to have an adverse effect upon the sensitivity of the methods for determining mass differences.

1. Sensitivity of the Method

An extensive series of observations have been made on a model basis which provide information regarding the overall sensitivity of the present method, as well as some information regarding the extent of systematic errors involved in it. The results of these studies have been reported and discussed elsewhere (120), and therefore shall only be considered here briefly.

The model experiments were carried out on a sheet of fused quartz 1 cm in length and 0.5 cm in breadth. One half of this sheet was 161 microns thick and possessed a plane parallel tolerance of less than half a wavelength of visible light. The other half of the sheet was wedge-shaped, its thickness decreasing from 161 to 50 microns in 5.0 mm. It should be noted that the linear absorption coefficient of this quartz is 81.0, while that of most fetal bone is 85. Thus, the use of this material as an experimental object seems quite justified for comparative technical studies.

The *reproducibility* of the densitometric measurements was assessed by making multiple determinations on the image of the plane parallel portion of the quartz in several microradiograms whose photographic densities ranged between 0.5 and 0.7. The value of the linear absorption coefficient calculated from these readings was 81.0 ± 1.3. Here, the standard deviation provides a measure of the methodical reproducibility.

The *sensitivity* of the densitometry was estimated on microradiograms of the wedge-shaped part of the quartz, and was expressed as the smallest

difference in mass (as reflected by altering the thickness of the otherwise homogenous quartz sample) which could be detected as a change in light transmission. At an average thickness of 100 microns, the densitometer registered changes in light transmission corresponding to variations in mass of ± 1.5 per cent. It should be noted that the conditions of photometry in these studies were similar to those used in the analyses of fetal bone.

The *thickness determination* used in the present investigation naturally decreases the sensitivity of the method to some degree. In order to assess the influence of this determination upon the entire method, a series of thickness determinations were done on fixed points in the wedge-shaped portion of the quartz, as well as on equidistant points along the slope of the wedge. Densitometry was subsequently performed on the microradiographic images of these points, and linear absorption coefficients were calculated according to the thickness determination for each. The resultant values were respectively 81.0 ± 1.7 and 81.3 ± 3.3, depending upon whether the thickness was determined on a fixed point or on equidistant points.

In an effort to measure *the accuracy of the combined techniques* of microradiography and densitometry, the results of the linear absorption coefficient determination made by the latter methods were compared with those obtained by an entirely independent method. Monochromatic x-rays of 1.54 Å wavelength, provided by a crystal monochromator, were passed through the plane-parallel portion of the quartz specimen. The transmitted x-ray beam was then recorded by a Geiger-Müller tube coupled to a count-rate meter and chart recorder, rather than by a photographic emulsion. The average results of 10 such determinations indicate that the microradiographic-densitometric method yields slightly higher values for the linear absorption coefficient, i.e., 81 as compared to 78 by the independent method, a difference of approximately 3 per cent. This variation may be attributed for the most part to the presence of a small longer-wavelength component in the Ni-filtered radiation, used in the microradiographic study. Essentially there appears to be a good agreement between the two methods.

The experiments cited above thus indicate that the technique employed in this study provides information regarding mineralization in absolute terms, an possesses a degree of accuracy closely approaching or equal to that given by other methods of relative measurement using microradiograms of high photographic densities (85).

2. Biological Significance of the Findings

Like all biological material, bone exhibits large natural variations, so that the standard deviations listed in Tables I through III thus reflect these variations as well as the methodical ones discussed above. The relatively

low value of the standard deviations in Table I and II indicate that the linear absorption coefficient calculations are rather precise.

This precision is reduced, however, in the data presented in Table III, because of increased methodical and biological variation. Despite the larger errors involved, the data in Table III still provide valuable information, especially regarding the earlier stages of the mineralization process. Since large variations in the data presented in Table III, as well as the somewhat reduced final level of mineralization (compare with Table I) are undoubtedly due to inhomogenieties in the specimen, it was concluded that more indicative information might be obtained by comparing the highest single determination observed in each point. When these values (Table III) were plotted, the resultant curve possessed the same shape as that illustrated in Figure 19, but the final level of mineralization was seen to be approximately 10 to 15 per cent higher than the average values. The ultimate value attained by the linear absorption coefficient under these conditions was 85, a figure which corresponds well with the original determination made on mature fetal bone (Table I).

The higher level of mineralization observed in the diaphyseal cross sections of the bone is probably explained by the influence of the hypermineralized zone appearing in the primitive periosteal collar. This structure corresponds to the "Grenzlinie" of the German literature (121). It constitutes the original limit between the embryonic periosteum and the cartilagenous bone model, and later in development marks the dividing line between periosteal bone on the one side, and endosteal or endochondral bone on the other. It bears a resemblance to cementing lines in older bone, which have also been shown to become hypermineralized (2).

Mature fetal bone attains two different levels of mineralization, the first with a linear absorption coefficient of 85, which represents most of the bone formed during the first half of intrauterine life. The second level reaches a value of just over 100, and becomes progressively more common in periosteal bone during the latter stages of fetal life. A similar difference in the level of mineralization has been observed in growing rabbit bone (85), where microradiographic study demonstrated the presence of calcified cartilage remnants possessing approximately 20 per cent higher x-ray extinction than adjacent bone. This finding is in good agreement with the absolute values presented in Table I.

The linear absorption coefficients obtained in these studies, as was discussed previously, result from the combined attenuation of the x-ray beam by apatite, as well as by the organic matrix and by water which may still be present in the sections. Some of the volume in the bone originally occupied by water is undoubtedly replaced by the plastic embedding material. How-

ever, it has been shown that the linear absorption coefficient of methyl methacrylate is very similar to that of water, so its presence should not introduce an error.

The influence of the organic material of the bone on the total x-ray absorption has been studied in detail by Amprino (1). By performing absorption studies both before and after microincineration of the bone structures possessing different levels of mineralization, this investigator showed that the organic material does not have any significant effect on the absorption ratios between the differently mineralized areas. Davies and Engström (29), using the interferometric method on dehydrated bone, were not able to discern any differences in the total content of organic material in bone of different levels of mineralization. Both of these studies support the concept that minerals are deposited at the expense of water content. It is known that the water content of bone decreases with age (17), while the overall level of mineralization increases.

The specific gravity of dried bone is about 1.3 (93). Knowing also that the specific gravity of calcium-hydroxy-apatite is about 3.1 (34), it is possible to deduce the approximate proportions of mineral and matrix in fetal bone from the mass absorption data given in Figure 3. Figure 20 illustrates the empirically calculated x-ray extinction values for different proportions of apatite and organic matrix, as well as for apatite alone. It is seen that in mature fetal bone, the x-ray extinction of which is 0.82, the mineral part occupies approximately 30 per cent of the volume, the remainder being made up of organic material and water. The true apatite extinction, however, is seen to be some 5 to 10 per cent less than the value obtained for whole bone. This difference might be expected to become accentuated in less mineralized bone where the non-mineral fraction takes up proportionally more of the volume, and thus contributes relatively more to the observed x-ray absorption.

The linear absorption coefficient for adult bone, as given in Table I, indicates a volume composition of almost exactly one-third apatite. This value corresponds very well with the specific gravity determination on adult bone done by Davies and Engström (29), using the microinterferometric technique. These authors computed the average density for dried human bone to be 1.9. Calculating from the specific gravity of bone components cited above, this density corresponds to a volume composition of one-third calcium-hydroxy-apatite, the remainder being organic matrix and water.

Determinations of the volume composition of fresh bone (96) show that the ratio of ash: matrix: water is 16.7: 20: 15. Thus the volume of the bone mineral constitutes just slightly less than one-third of fresh bone, again in good agreement with the present findings.

The close parallelism in the results of these independent methods of mineral volume determination with the present microradiographic determinations emphasizes the relatively minor role of the organic matrix and water in the x-ray absorption measurements.

In order to estimate the quantitative changes in growing bone, many authors have applied chemical analytical techniques to whole mammalian bones of different ages, or to individual portions within the same bone having a relatively different age. These studies have shown that the ratio of phosphorus to nitogen increases with bone age (99, 102), reflecting the known increase in mineral content. In fresh bone, the ratio Ca: P increases with bone age (21, 22, 26, 28). This fact is interpreted as being due to the presence of excess phosphorus, bound to protein, in new bone, since the Ca: P ratio remains constant in ashed bone regardless of age (26). Typical values for the total amount of calcium in the dried epiphyseal and diaphyseal portions of embryonic dog bone have been given as 12.8 per cent and 16.9 per cent, respectively (17). The total amount of organic material in cor-

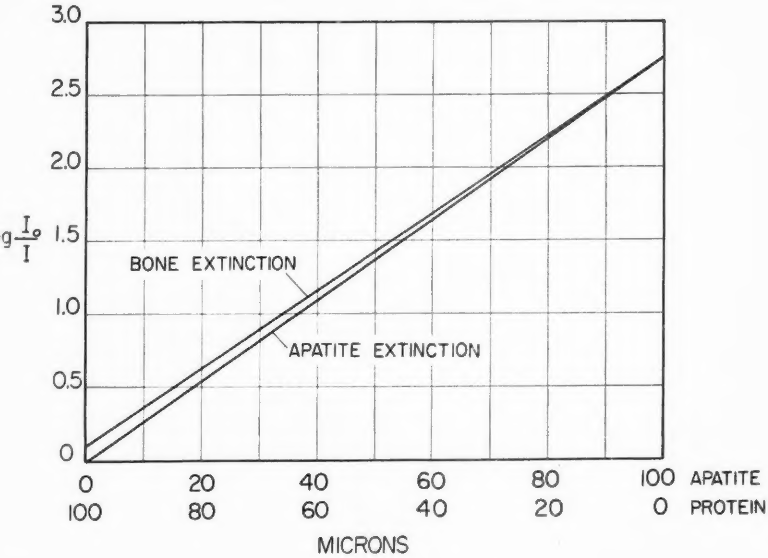


Fig. 20. X-ray extinction of 1.54 Å radiation in bone of different mineralization (expressed as the volume ratio, apatite: protein), as compared to the true apatite extinction. The curves are drawn from values obtained empirically for mass absorption coefficients in Fig. 3. The specific gravity of apatite is assumed to be 3.1, and that for dried bone protein to be .3. It is seen that the organic material is relatively more responsible for the observed extinction of bone with low mineralization.

responding regions of post-natal bone have been estimated to be 70 and 63 per cent (110). Since all of these studies have been undertaken on gross bone structures, there has been no possibility of investigating the mineral content in microscopical structures, nor of gaining an accurate estimation of the true age of the bone studied. Thus, they provide only fragmentary information relating to the local quantitative changes which may occur in the calcified tissues during growth and mineralization.

By the use of a special transplantation technique in adult rabbits, Dallemage (27) succeded in obtaining new bone samples of a rather well defined age and in sufficient quantity for chemical analysis. He showed that the calcium and phosphorus content in the ashed samples increased rapidly during the first 15 days of bone growth, while from that time to the thirtieth day, when a definite level was reached, the rate of increase was less rapid. Despite the difficulties of this technique, his studies have provided valuable information about the rate of mineral deposition and which could be expressed in absolute terms.

Microradiographic and radio-isotopic experiments performed by Lacroix (73) on developing Haversian system in the dog indicated that initial mineralization proceeded rapidly. But before full mineralization had been attained, as judged microradiographically, the rate of mineral deposit decreased to such an extent that it could not be appreciated in radio-calcium autoradiograms. Later, the same author (74) demostrated by autoradiographic analysis of radiosulfur uptake that complete formation and mineralization of Haversian systems in the dog required approximately six weeks. This result confirmed the earlier conclusion of Arnold and Jee that, as judged by radio-calcium autoradiograms, the complete mineralization of Haversian systems required more than three weeks (5).

Both of these studies were carried out on Haversian systems, which cannot be considered to be homogeneous structures, and are therefore not strictly comparable to the fetal bone investigated here. However, the general similarity in the estimate of the time required for mineralization in Haversian systems and that of the fetal primary periosteal bone collar is too striking to be overlooked.

Investigation by quantitative microradiographic methods of bone transplants in rabbits and dogs (61) has also provided values for the rate of mineral deposition in transplants, similar to those obtained here for fetal bone.

From all the foregoing observations, it is tempting to conclude that all newly-formed bone retains a capacity for rapid growth and mineralization quite comparable to that of the fetal condition, regardless of the actual age of the organism.

IV. X-ray Crystallographic and Polarized Light Microscopic Studies of Mineral-Matrix Ultrastructure

A. Introduction

In 1925, Sir William Bragg suggested that x-ray diffraction studies of crystalline colloidal particles were capable of providing information regarding the internal structure of the particles, as well as regarding their shape, their average size, and their tendency to become oriented in the colloidal system. The apatite crystallites of bone constitute a crystalline system, and have been studied extensively during the last 25 years by diffraction techniques. The potentialities of the method forseen by Bragg, have all been succesfully exploited, and the results of these studies now provide the major share of our present knowledge of the ultrastructure of bone.

The crystalline nature of bone salt was first established by de Jong (65) in 1926, who showed that bone gave an x-ray diffraction pattern similar to that of naturally occuring minerals in the apatite group. Although opinions regarding the exact chemical nature of the bone salt are many and varied (for a survey of this field, the reader is referred to reference 3) the most generally accepted one is that of calcium-hydroxy-apatite, $Ca_{10}(PO_4)_6(OH)_2$ The unit cell (the smallest repeating unit in the crystal) of the bone crystallites has been shown to have a hexagonal shape, the internal structure of which has been established by x-ray diffraction (9, 18, 54, 119). The axial dimensions of the unit cell have been measured with an accuracy of better than 0.02 Å. The a-axis has a length of 9.42 Å, while that of the c-axis is 6.88 Å (18).

The average size and shape of the entire crystallite has been studied by high-angle and low-angle diffraction procedures (18, 45, 65, 111). According to these investigations, the apatite crystallites in bone are rod-shaped particles, whose average dimensions are 230 by 65 Å. High-angle x-ray diffraction has been utilized to establish the fact that the c-axis of the crystallites in bone is approximately parallel to the long dimension of the particles (111), and has also been used to show that the long dimension of the crystallites in

bone is oriented in the same direction as the collagen fibers (24, 56, 1[illegible]1). These findings have been confirmed in small-angle x-ray particle scatter studies of intact bone (45).

The relationship of the apatite crystallites in bone to the underlying matrix was also investigated by Schmidt in 1933 (105). Using the polarized light microscopy, this author demonstrated that the apatite crystallites were oriented with their long axis parallel to that of the collagen fibers associated with them. It is of special interest to note that a series of brilliant deductions by this same investigator in 1923 (104), based upon polarization microscopic observations of dental enamel, suggested that the mineral was crystalline in nature, that the particles were elongated, and that they demonstrated a preferential orientation. This work was carried out several years before the first x-ray diffraction studies revealed the crystalline nature of mineral deposits in bone and teeth. The fact that all of Schmidt's original suggestions have been borne out by independent investigations constitutes a great tribute to his ingenuity and to the utility of polarization microscopy in this kind of work.

More recently, the application of electron microscopic methods to the study of bone mineral-matrix ultrastructure (8, 50, 62, 63, 67, 97, 107), has confirmed that there is a close structural relationship between the apatite crystallites and the underlying collagen fibrils, and that the regular repeating 640 Å periodic structure of the fibril is involved in this relationship. This latter finding confirms what had already been suggested on the basis of x-ray diffraction evidence (20).

Our present concept of the ultrastructure of adult bone thus indicates a system in which the elongated apatite crystallites are in some way bound to the oriented collagen fibrils, in close association with the fibril's repeating structure, and with their c-axis as well as their long dimension parallel to the long axis of the collagen fibril.

However, there is very little information available concerning the ultrastructural characteristics of the apatite crystallites in bone during its formative stages. It therefore seemed of great potential interest to apply the techniques of x-ray diffraction to determine whether any ultrastructural differences do occur at this time, and with the ultimate goal in mind of attempting to relate them to the overall dynamics of fetal bone growth.

The following section, then, concerns itself with investigations of some of the physical characteristics of the apatite crystallites including their orientation, their average size, and their relationship to the organic matrix during fetal bone formation.

B. Methods

1. X-ray Diffraction Applied to the Inorganic Fraction

A detailed discussion of the theory and techniques of the crystallographic analysis is beyond the scope of this presentation. For a complete account, the reader is referred to the standard reference works listed in the bibliography (51, 69), from which the brief resumé which follows has been derived.

When a narrow monochromatic x-ray beam passes trough a crystalline medium, it may, under certain conditions, be reflected from one or several different groups of the equidistant atomic planes which constitute the crystalline lattice. The conditions for x-ray diffraction are determined by the Bragg law,

$$n\lambda = 2d \cdot \sin \Theta \qquad [7]$$

where n is a whole number representing the order of diffraction, λ is the wavelength of the x-ray beam in Å, Θ is the glancing angle formed between this beam and a specific set of equidistant (and therefore parallel) reflecting atomic planes within the crystal, and d is the interplanar distance in Å characteristic of this particular set of atomic planes.

According to this relationship, the glancing angle (Θ) bears an intimate relationship to the interplanar spacing (d), and at any given angle of Θ, reflections occur only from that particular set of atomic planes whose interplanar spacing satisfies the Bragg law. Alteration of the glancing angle, by changing the position of the sample relative to the incident x-ray beam, may subsequently cause diffraction of the incident beam by other groups of atomic planes, provided that their interplanar spacing bears the proper relationship to the glancing angle. Ultimately, it is thus possible to obtain diffractions from all of the different groups of atomic planes present in the crystal structure.

Diffraction is a type of reflection of the incident x-ray beam by the atomic planes, so that the glancing angle is one half of the angle between the undeviated x-ray beam and the diffracted beam from a particular group of planes. Measurement of the latter angle thus gives the glancing angle. Since the glancing angle for a given x-ray wavelength can be accurately determinded, the diffraction technique provides a precise measure of the different values of the interplanar spacings present in the crystal. From the latter information, one is able to deduce certain crystallographic properties of a crystalline material.

In a system containing a large number of randomly dispersed small crystallites, the various crystallographic planes will also be randomly distributed, and hence the chances for a given group of planes to be in a

"reflecting" position is great. This is the principle of the powder technique, in which the diffracted x-ray beams have the form of a series of concentric cones, the common apices of which lie in the sample. Their individual apical angles are, of course determined by the interplanar spacing of that particular group of reflecting planes which give rise to them. In a diffractogram of a randomly oriented system of crystallites, the intensity of each of the diffracted cones is uniform throughout its circumference. On the other hand if a diffraction is carried out on a sample whose individual crystallites tend to orient themselves in a particular direction, the intensity of the diffracted x-rays is not uniform and so called "fiber" diagrams are obtained. When such a diffractogram is recorded on a flat film the photographic density will therefore tend to be greater in certain, diametrically opposed regions on the circumference of the circle. The appearance of zones of increased density in a diffraction image are therefore indicative of orientation of the crystallites.

As was stated in the introduction to this section, the c-axis of the apatite unit cell is approximately parallel to the long axis of the crystallite. A diffractogram showing the orientation of the c-axis will thus also demonstrate the orientation of the entire crystallites with reference to their long dimension.

The most convenient measure of orientation of the c-axis is provided by the (00'2) reflection of apatite. This component of the diffraction pattern originates in a specific group of reflecting atomic planes (identified as the (00'2) planes) which lie perpendicular to the c-axis of the unit cell. It has already been seen that changes in the spatial orientation of the entire crystallite will cause alterations in the character of the diffractogram. As the longitudinal axis of the entire crystallite tends to become more and more oriented in one direction, so, too, will the c-axis of the unit cell. Ultimately at certain points about the circular image of the (00'2) reflection of apatite, the photographic density will become increased, while at other points it will be reduced. The ratio of the increase in density to the decrease in density thus provides an indication of the degree of orientation, while the actual position of the areas of increased density indicates the spatial direction in which orientation of the long dimension of the crystallites has occurred.

Since the mineralized structures in fetal bone are extremely small, and since differences in their anatomical orientation are apt to occur within very small areas, it is important to use as fine an incident x-ray beam as possible in these studies. For if the x-ray beam covers such a large area of the sample as to give rise to reflections from adjacent structural systems of different orientation, the resulting diffractogram may appear to be unoriented, in spite of the existence of many small and well-oriented (but as units randomly dispersed) areas within the sample.

In the present study a total of more than 100 microdiffractograms were made on the same fetal samples which were used for microradiography. A Chesley microdiffraction camera (23) was used, in which the x-ray beam was collimated to a width of 20 microns. Nickel-filtered copper radiation was generated at 40 kV and 20 mA. The sample-to-film distance was 15 mm.

Visual assessment of the degree of orientation is very often hazardous due to variable differences in contrast, as well as to the presence of background fogging of the film. Therefore, densitometric evaluation of the diffractograms was performed. Continuous densitometric readings were recorded across the (00′2) reflections of the diffractograms, first through the two regions of maximum density, and then through the regions of least density at right angles to the former. Corrections for background fogging were then made on the recording chart.

The ratio between the mean value of the two maximal and the two minimal densities from each image was then considered to be a measure of the degree of crystallite orientation. Since the density response of the emulsion was essentially linear to x-ray intensity in the density ranges used, this estimation was valid, although only approximate, and certainly provided more reliable information than could visual observation.

2. X-ray Diffraction and Polarization Microscopy Applied to the Organic Fraction

a. *Diffraction Studies of Collagen:* In view of the fact that the structural organization of apatite crystallites in all probability is intimately bound up with that of the collagenous matrix, some of the structural properties of collagen in fetal bone were also investigated. Collagen is a semicrystalline protein and gives rise to a diffraction pattern with three well-defined high-angle reflections, which correspond to interplanar spacings of 2.8 Å, 4.5 Å and 11—15 Å, respectively. It is also known to exhibit a low-angle reflection, arising in its characteristic 640 Å structural period. This latter reflection, however, is recorded accurately only by diffraction cameras possessing very high resolution and was not dealt with in the present investigation.

Since in diffraction studies, as in microradiographic studies, the sample thickness bears a close relationship to the linear absorption coefficient of the material which is being analysed (Formula I), the collagen studies had to be done on samples approximately 1 mm in thickness. Bone samples of this thickness were decalcified until microradiographic controls showed no sign of residual bone mineral, and, in order to minimize the influence of periosteal collagen, the periosteum was removed. The diffractograms were

recorded on Ilford Industrial G. film in a plane-film camera, with a sample-to-film distance of 26.4 mm. Nickel-filtered copper radiation was employed, and the beam width was 250 microns.

b. *Polarized Light Studies of Collagen:* The large mass of material required for diffraction studies of collagen precludes the investigation of isolated microscopial structures. Hence, the fiber direction of collagen was studied in specific microscopic regions of the developing fetal bone by polarized light microscopy.

Collagen is uniaxially positively birefringent, and is thus visible between crossed Nicol prisms in the microscope. If the fibers are oriented in one direction and the incident polarized light rays are perpendicular to this direction, changes in the intensity of illumination of the fibers during rotation of the sample follows a distinct pattern. From this, the general orientation of the fibers may be decuced. (For a detailed review of this method and its interpretation, se reference 106). In some cases, visual observation of the fibers may also be possible at high magnification, and thus provide an independant method of determining the fiber direction.

The samples used in this part of the investigation were the same as those used for diffraction studies of the mineral part, i.e., 100 micron thick plastic-embedded sections. Examples of these were examined after removal of the plastic, both intact, as well as after demineralization.

3. Crystallite Size Determination

While there is reliable evidence regarding the definitive dimensions attained by the apatite crystallites in adult bone, little is known about their growth in developing bone. This problem has been approached in the present investigation by use of two x-ray methods for particle size determination, one based on the "line-broadening" effect, the other on the low-angle particle scatter caused by the crystallites.

a. *Studies of the Diffraction Line-broadening:* When the individual crystallites in a polycrystalline compound are less than 10^{-4} mm. in their longest dimension, equidistant atomic planes within every crystallite are so few in number that their specific diffraction lines tend to become broader and less sharply defined. Measurement of the extent of this phenomenon, or line-broadening, thus provides one method for particle size determination. As the c-axis of the apatite crystallite is approximately parallel to the long dimension of the crystallites, changes in the width of the (00'2) reflection may thus be a measure of their *overall length*.

Estimations of the (00'2) line width of apatite in fetal bone were carried out with the aid of a Philips Geiger Counter Goniometer

(PW 1050), using nickel-filtered copper radiation at 40 kV and 20 mA. The advantages of this electronic method of analysis over the older photographic methods have already been discussed by others (69). Bone samples were dried to a constant weight, and after as much as possible of the non-bony elements had been removed by microdissection, they were pulverized to a fine powder. The diffraction analysis was then made on a layer of the powder 3 mm in thickness.

The distribution of x-ray intensity in the resultant (00′2) reflections from each sample were then recorded at angular intervals of 0.05°. In order to give a reasonable statistical accuracy to the readings, a total of 6400 counts were recorded for each interval, and the actual intensity was recorded on a chart in terms of the number of counts per unit time. The intensity profile of the reflection was then plotted (Figure 29) and the half-width calculated, i.e., the angular width at half-maximum intensity. The latter value was then corrected for mechanical errors introduced by the instrumentation as well as for errors introduced by the fact that the incident x-ray beam contained the K_α doublet. The resultant value thus represented the pure width of the diffraction line and was then used to calculate the long dimension of the apatite crystallites according to the Scherrer formula (69):

$$D = \frac{K\lambda}{\beta \cdot \cos \Theta} \qquad [8]$$

in which D is the dimension of the crystallite, K is a constant, λ the x-ray wavelength in Å, β the half-width of the pure diffraction line, and Θ is the glancing angle.

The errors associated with the entire method are due to inaccuracies in the plots, and to the calculations involved in deriving the pure line width. Inaccuracies in the plot were minimized by making a large number of counts for each measured point. The error of the correction of the raw data to obtain the pure diffraction width, is related to the ratio of the broadening brought about by the instrument itself to that of the total broadening visualized. The high degree of precision offered by the instrument utilized here, however, did not contribute significantly to this ratio (0.2—0.3), and thus inflicted only a minor error on the method. The total error of this method applied to the (00′2) reflection of apatite has previously been given as ± 10 per cent on the basis of experimental studies (18, 75), and by theoretical estimations (69).

b *Studies of the Low-angle Scatter:* The intesity distribution in the low angle particle scatter, i.e., the x-ray scatter close to the transmitted undeviated beam, from randomly oriented particles, depends upon the radius of gyration $\overline{R}$ of the particles of colloidal dimensions. The latter

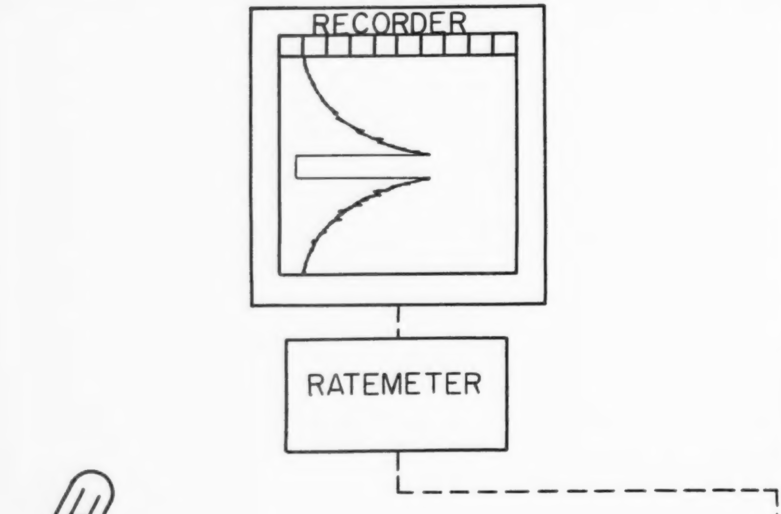


Fig. 21. Schematic plan of the apparatus employed for low-angle scatter studies. The Geiger-Müller tube is moved at a constant speed perpendicular to the undeviated x-ray beam.

characteristic is closely related to the absolute size of the scattering particles, so that studies of the intensity distribution within the low-angle region provides another way of obtaining information about particle size.

Guinier (51) has shown that a plot of the relationship *log I* versus ε^2 in which I is the intensity of the scattered radiation at any point from the undeviated beam, and ε is the angular distance of that point from the beam, bears a relation to the average size of the particles according to the following formula:

$$\overline{R} = 0.416 \lambda \sqrt{\alpha} \tag{9}$$

in which $\overline{R}$ is the radius of gyration of the particles of any shape, λ is the wavelength in Å, and α is the angular inclination of the log I/ε^2 plot.

In Figure 21 is shown a diagram of the apparatus employed for study of

particle scatter. The x-ray tube was operated at 40 kV and 20 mA, and the copper radiation was then monochromatized by reflection in a quartz crystal so as to provide the pure Cu Kα line radiation (1.54 Å) in approximately parallel bundles. The sample to detector distance was 110 mm.

C. Results

1. X-ray Diffraction Studies of the Inorganic Fraction

Wherever mineral deposits appeared in the fetal skeleton, the diffraction pattern was that of calcium-hydroxy-apatite. No traces of other crystalline salts were ever noted. However, since the Chesley camera is not ideally suited for qualitative work, it was considered entirely possible that small amounts of other crystallites might have been present in the samples without being detectable by these diffraction studies. In order to eliminate this possibility, bone powder diffractograms were recorded with the Philips Geiger Counter Goniometer, which has a much higher resolution than conventional photographic methods of detection. In no samples, ranging in age from 15 weeks to full term, were any crystallite components other than the apatite detected.

Incineration to 900° C for one and a half hours caused the diffraction lines from the samples to become sharper and thinner, since this treatment increases the size of the particles. In some areas, corresponding to very newly formed bone, the diffraction patterns following incineration also showed the presence of tricalcium phosphate. However, because of their very small size, and extreme fragility after incineration, it was not possible to make systematic microdiffraction studies of these areas. It should be emphasized that only the most recently formed parts of the bone gave the pattern for tricalcium phosphate, and powder diffractions made on the incinerated diaphyseal portion of young bone (15 weeks) exhibited only the pattern characteristic of apatite. Older incinerated bone also demonstrated only the apatite pattern.

The diffractograms from the youngest sample which contained mineral deposits in the femur, a 9.5 week old fetus, gave a slight but definite sign of orientation in some areas of the metaphyseal and diaphyseal portions of the periosteal bone collar. In part this preferred orientation in the crystallites was directed along the long axis of the bone, but tendencies toward deviation from this axis were commonly observed. Both calcified cartilage and the epiphyseal parts of the periosteal bone collar gave unoriented diffraction patterns (Figure 22, A).

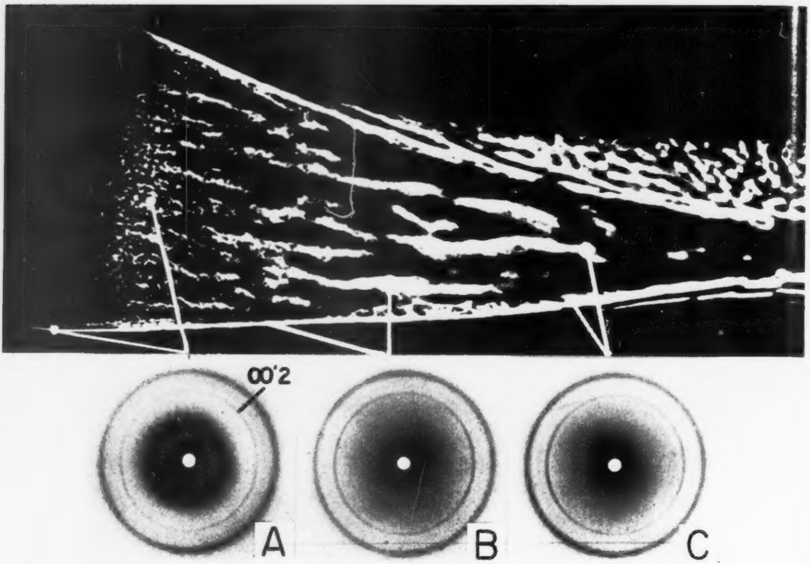


Fig. 22. Distal end of the femur from a 17-week-old fetus in longitudinal section, with corresponding x-ray microdiffractograms, A, B, and C.

Note in A the pronounced influence of the organic matrix on the diffraction pattern, as reflected by increased photographic density in the region of the beam stop (center). There is no sign of crystallite orientation in the (00'2) reflection of bone apatite. Diffractograms B and C illustrate increasing orientation of the (00'2) reflection in the longitudinal axis of the bone.

Diffraction on older samples, 13 to 40 weeks old, gave somewhat better oriented patterns directed as before, along the long axis of the bone. The degree of orientation, however, frequently appeared to vary in closely adjacent structures. Periosteal and endochondral bone at these ages, showed a similar degree of orientation. Comparison of the overall degree of orientation within this age range did not demonstrate any appreciable difference. The densitometric analyses did demonstrate, however, that the degree of orientation in fetal bone never attains the high levels encountered in adult bone. The highest orientation figures (diffractogram density ratios) obtained for fetal bone in this study were in the order of 2.5 to 3.5, while in adult bone, values of 4 to 6 were not uncommon. The only structures in fetal bone that never showed any sign of orientation during development were the calcified cartilage and the newly-formed endochondral and periosteal bone at the epiphyseal ends.

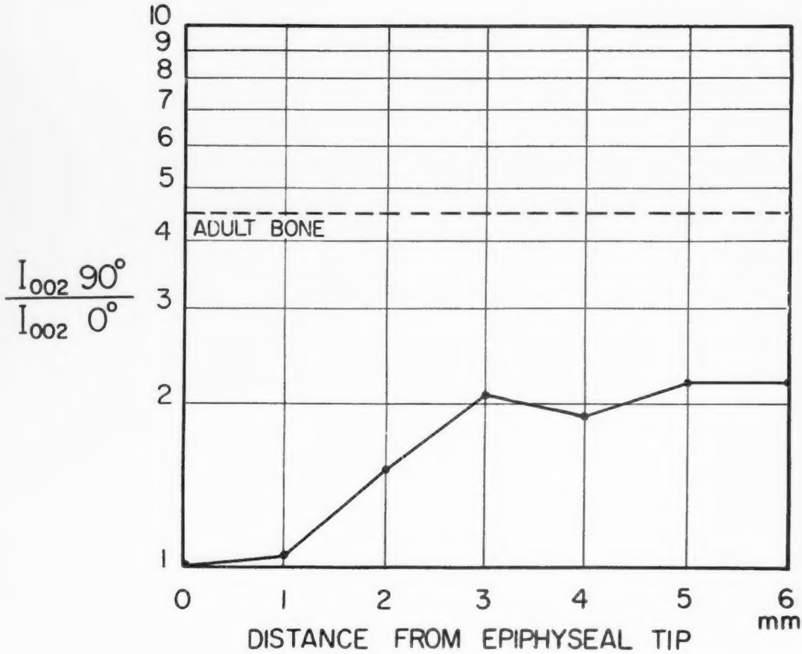


Fig. 23. Densitometric evaluation of the degree of orientation in the primary periosteal collar of the sample viewed in Figure 22. Diffractograms were made at 1 mm intervals beginning at the point in the epiphyseal end of the structure at which mineral deposits were first apparent.

In order to estimate the role of maturation upon the orientation of the crystallites, diffractograms were taken in series along the primary periosteal bone collar, extending from the epiphyseal tip of this structure down into the diaphyseal region. The relative degree of orientation was then estimated densitometrically for each point, and these values were then plotted against the data regarding length increment in the distal femur available from the microradiographic studies already described. Figure 23 illustrates this relationship in a 14 week-old fetus. It is evident that there is no sign of orientation in the very first bone laid down, but that soon thereafter it begins to be apparent, and quickly attains a "standard" value for fetal bone.

Cross sections of the mid-diaphyseal part of fetal bone exhibited unoriented patterns for the most part, but in some of the older specimens periosteal bone layers showed a slight degree of tangential orientation.

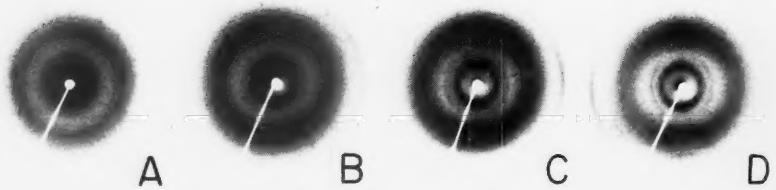
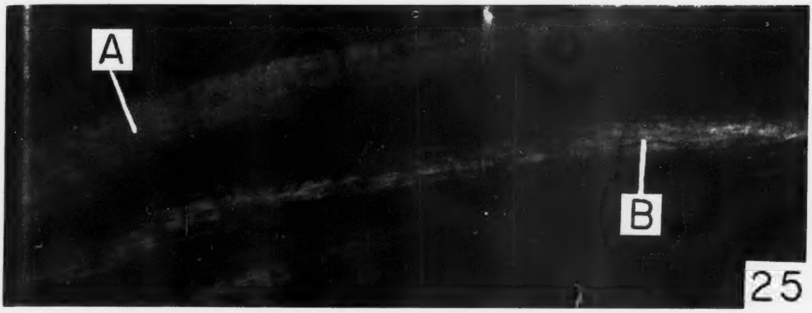


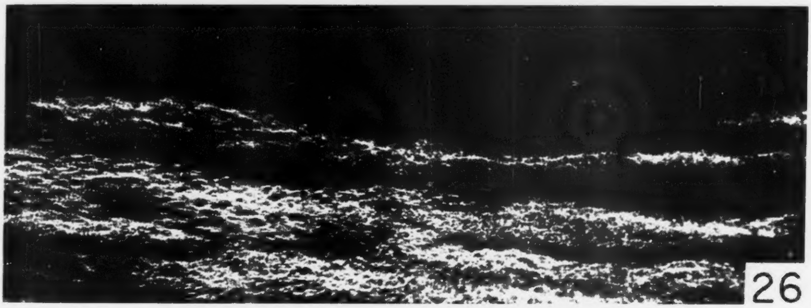
Fig. 24. Collagen diffractograms from 9.5-week-old (A), 10.5-week-old (B), and 40-week-old (C) fetal femurs, and from adult bone (D). Once the orientation is apparent at 10.5 weeks (B), there does not seem to be any significant increase in the fiber orientation.

2. X-ray Diffraction and Polarized Light Microscopic Studies of the Matrix

Diffractograms made of bone collagen obtained at 9.5 and 10.5 fetal weeks, at full term, and from the adult human are illustrated in Figure 24. Examination of the figure reveals that once orientation is apparent, the high-angle diffraction pattern does not indicate much increase in orientation with progressing age. Instead the orientation remains on a more or less even level which is maintained right up to birth and into adult life. The diffractograms did not indicate any significant differences in the molecular structure of the collagen during bone development.

Polarized light studies on the fibrillar orientation of the microscopical units of structure served to confirm the diffraction results. In general, the direction of the collagen fibers tended to be parallel to the long axis of the bone. At the epiphyseal tip of the primary periosteal collar, moreover, the fibers in the bone had almost the same degree of orientation in the longitudinal direction of the bone as did the collagen of the periosteum. (Figure 25, B) The remainder of the bone collagen appeared to have a more variable orientation at the microscopic level (Figure 26), although it retained a tendency to be longitudinally oriented .In the epiphyseal cartilage (Figure 27) of the longitudinal bone sections, there appeared collagen fiber bundles possessing a striking degree of longitudinal orientation (Figure 28, B), lying between the columnar rows of hypertrophic cartilage cells in the growth zone. The zone of provisional calcification of cartilage did not exhibit any birefringence (Figure 28, C), while that of the articular portion of hyaline cartilage (Figure 28, A) was variable but mostly directed at right angles to the long axis of the bone. Close examination with varying positions of the sample, suggested that the collagen fibrils of the articular zone, although not especially well oriented, tended to connect structurally with the very well oriented fibers seen in the zone of cartilage hypertrophy.





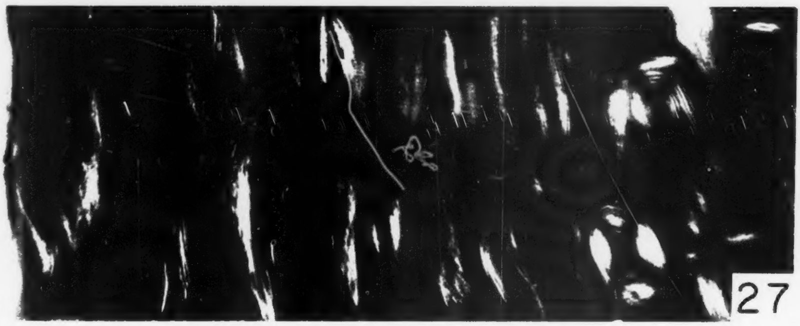


Fig. 25. Undecalcified section of the epiphyseal tip of the primary periosteal collar from an 18-week-old fetus, viewed in polarized light. Magnification, x 130.
Periosteal collagen (A) is well oriented in the longitudinal direction of the bone. The fiber direction of poorly mineralized bone in the epiphyseal tip of the collar (B) is similar to that of the periosteum.

Fig. 26. Same sample as in Fig. 25, after decalcification, with the metaphyseal part of the bone viewed in polarized light. Magnification, x 130.

Continued

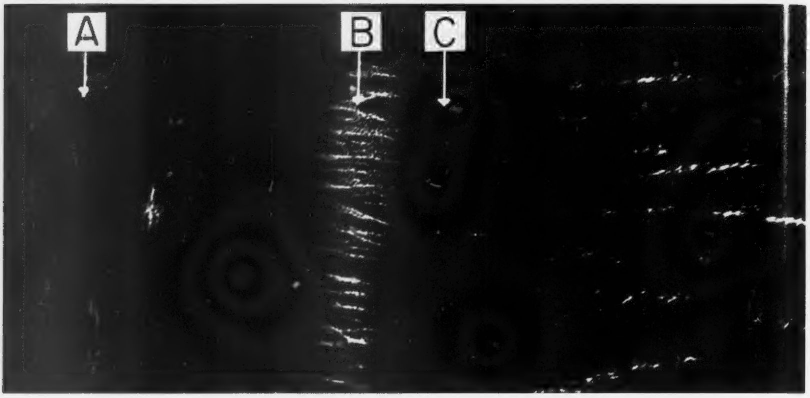


Fig. 28. Decalcified longitudinal section from the distal epiphysis of the femur from a 30-week-old fetus, viewed in polarized light. Magnification, x 70. A: Fibers in hyaline cartilage perpendicular to the long axis of the bone; B: Zone of longitudinally oriented fibers, corresponding to the basal cartilage layers in the region of cartilage column formation; C: Zone of provisional calcification, in which no oriented collagen is seen.

Cross sections from the mid-diaphyseal part of most bones did not show any preferred orientation of collagen, their birefringence being significantly lower than it was in the longitudinal sections. No birefringence of periosteal collagen was ever seen in the cross sections, indicating a very strict longitudinal orientation of the fibers in the periosteum. Cross sections of older samples of bone demonstrated tangential orientation of some collagenous elements (Figure 27). These latter areas corresponded to those where tangential crystallite orientation had been noted previously.

3. Crystallite Size

a. *Line-broadening Effect:* Since the Geiger Counter diffractometric method requires samples of approximately 150 cubic millimeters volume, several specimens from the younger age group were pooled. In the pooled sample, the average age of the specimens was 15 weeks, the range being 1[illegible].5

Continued

The woven character of the collagen fibers in the metaphysis is well illustrated, and is in striking contrast to the precise longitudinal allignment of the fibers at the epiphyseal tip of the collar (Fig. 25).

Fig. 27. Decalcified mid-diaphyseal cross section of the full-term fetal femur, viewed in polarized light. Magnification, x 130.

The newly-formed Haversian systems exhibit a typical lamellation, and the characteristic cross of birefringence (lower right).

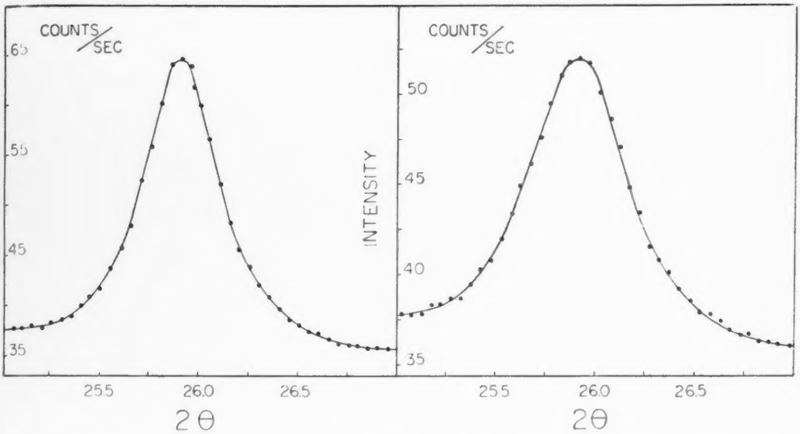


Fig. 29. Geiger counter, diffractometric registration of the (00′2) line profile of bone apatite in powders of mid-diaphyseal femoral bone samples from a full-term infant (left), and from a 15-week-old fetus (right). The counts were made at angular intervals of 0.05°. The line broadening effect in the young bone sample is evident, and indicates a smaller average particle length.

to 16.5 weeks. Table IV presents the average longitudinal dimension of apatite crystallites in the diaphysis at this stage of development, compared to their average length in epiphyseal and diaphyseal samples taken from 30 week and fullterm specimens. The corresponding half-width values calculated from the intensity curves (Figure 29) of the diffractions are also presented.

TABLE IV.
Effect of Age on the Length of Fetal Bone Crystallites as Determined by Line-broadening of the (00′2) Reflection

Sample:	15 Week Diaphysis	30 Week Diaphysis	30 Week Epiphysis	40 Week Diaphysis
Half-width of the (00′2) reflection	0.57°	0.50°	0.57°	0.44°
Calculated long dimension of the apatite crystallites	158 ± 16 Å	183 ± 18 Å	158 ± 16 Å	217 ± 22 Å

The accuracy of the calculation and measurements was checked by repeating the observation on the 15 and 40 week specimens. The values obtained for average crystallite length from this second set of observations fell within

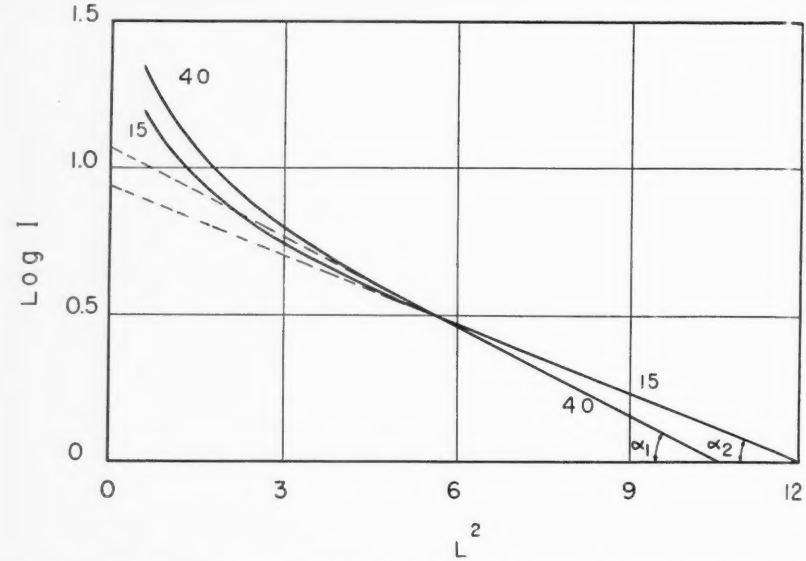


Fig. 30. Energy distribution within the low-angle region from the same powders as in Fig. 29, plotted as log I/L^2, in which I is the x-ray intensity, and L is the linear distance in mm from the undeviated beam. The measurements were made with the apparatus shown diagrammatically in Fig. 21. The steeper inclination of the main part of the curve from the full-term sample (40) indicates the presence of particles with a larger average radius of gyration than that of the 15-week sample (15). The similarity between the two curves close to the beam stop indicates that the largest crystallites of each specimen have approximately the same size.

4 per cent of those indicated in Table IV. Determinations made on adult bone showed that there was no significant change in the average length of the apatite crystallites after birth, the value for adult bone being 233 ± 23 Å.

b. *Low-angle Particle Scatter:* It is known that the line-broadening effect in diffraction can result from the presence in the sample of imperfect crystallites (69), i.e., those in which the internal atomic structure is not yet perfectly or regularly arranged. Since imperfections of this sort are frequently associated with small, not yet fully-formed crystallites, the possibility existed that in growing bone some or all of the line-broadening effect could arise from this cause, and thus yield erroneous values for the crystal length of apatite. Hence, it was considered advisable to confirm the above values by an independant method, the low-angle particle scatter technique.

The Guinier approximation (log I/ε^2) retains its exponential relationship to particle size only when all the particles in the system are identical. When the population of particles becomes dissimilar, the exponential relationship

is found to hold only in the region nearest the undeviated x-ray beam, which corresponds to the largest particles in the system.

Figure 30 illustrates the data plotted in this study from powder samples of the 15 week and 40 week specimens. Both of the curves exhibit a diminishing slope as the distance from the undeviated beam increases, thus indicating the presence of irregularities in size within the crystallite population. Comparison of the curves reveals that the overall slope of that representing the older sample is steeper, so indicating the presence in this sample of a relatively greater proportion of larger particles. However, closer to the undeviated beam, the slopes of the two curves tend to be the same, suggesting that the largest particles in both samples have approximately the same size.

The particle scatter method thus provides confirmation of the data obtained by the line-broadening studies, and indicates that the apatite crystallites tend to increase in length during fetal bone growth.

D. Discussion

Calcium-hydroxy-apatite is generally accepted to be the crystalline mineral material common to the normally calcified tissues of adult mammals, and is also the most common constituent of mammalian pathological calcifications (15). Opinions regarding the structural and chemical nature of the first bone salts laid down, however, have been at some variance.

Previous investigations have suggested on the basis of chemical analyses that salts other than calcium-hydroxy-apatite occur in newly-formed bone (76, 101, 103). The presence of phosphorus in excess, bound either to the protein matrix, or to the crystallite surfaces of the bone salt has been shown (21, 22, 28, 52). The possibility that the physical state of the first bone salt formed is amorphous, rather than crystalline, has been put forward on theoretical grounds (55, 60), and has recently been reiterated on the basis of electron microscopic studies of very young bone (63).

The result of the present studies contribute several observations which may be of some value in gaining a further understanding of the chemical and physical nature of newly-formed bone salt. The very youngest deposits of mineral which were detectable by the extremely sensitive microradiographic method gave only the characteristic pattern for calcium-hydroxy-apatite when examined with x-ray diffraction methods. This observation suggests that the first bone salt is deposited in the crystalline form, the internal crystalline structure of which is very similar to that seen in adult bone. Its quantitative chemical composition, however, may vary a good deal without

giving rise to noticable changes in its x-ray diffraction pattern. It is known (18), for example, that the calcium to phosphorus ratio of apatite may vary as much as from 1.3 to 2.0 without significant alterations in the diffraction pattern. This property of the salt has been attributed to the tremendous surface area presented by the very small crystallites, and the consequent capacity of surface absorption of various ions, including phosphate and carbonate. The greatest share of the observed variations in chemical composition of bone apatite are probably due to the presence of such surface-bound ions (7, 82).

While crystallography is thus not ideally suited for precise chemical analysis of bone salt, certain features of its chemistry can be observed by these techniques. Information regarding the calcium to phosphorus ratio (Ca: P) may be obtained with an increased degree of precision after the bone sample has been incinerated. It has been shown (59), for example, that incineration of bone samples from rats made rachitic by excessive dietary phosphorus, exhibit diffraction patterns of not only apatite but also of tricalcium phosphate, a crystal which contains relatively greater amounts phosphorus. Carlström (18) found that incineration at 900° C of salts with a Ca: P ratio of less than 1.67 (1.67 being the normal ratio for calcium-hydroxy-apatite) would exhibit varying degrees of transformation into crystalline materials relatively more rich in phosphorus. In the present study, only very recently formed bone showed this type of conversion upon incineration, and thus only this most newly-formed bone possessed a Ca: P ratio of less than 1.67. The normal ratio for calcium-hydroxy-apatite, or values exceeding this ratio, are attained very rapidly in fetal bone development.

The crystallographic data obtained in this investigation, then, seem to indicate that in the newly formed fetal bone the mineral component is crystalline and exhibits the pattern of calcium-hydroxy-apatite. The Ca: P ratio lies below a value of 1.67 at the very earliest stages of bone formation, but soon attains or exceeds this value. This latter finding is therefore in accord with chemical analysis of newly formed bone (21, 22, 28, 76), which demonstrated excessive amounts of phosphorus during earliest stages of bone formation.

Since the crystalline structure is readily recognized in the first detectable bone salts in the human fetal femur, an amorphous structural phase of the mineral, if it exists at all, must be of very short duration.

It is generally believed that collagen plays some role in orienting the apatite crystallites in bone (16, 19, 44, 56, 58, 92, 105). The collagen bundles in fetal bone are seen morphologically to be coarsely and irregularly arranged, so it is perhaps not surprising that the general degree of orientation of the

crystallites in fetal bone is less than that of adult bone, in which there is a fine-fibered and well oriented collagenous matrix.

The fact that the high-angle diffraction patterns of collagen in the fetal bone display a degree of orientation entirely comparable to that of the adult bone is an unexpected and rather astonishing finding, particularly in view of the striking differences in orientation visualized between them by polarization microscopy, and even in the light microscope. While this descrepancy is difficult to resolve, it seems likely that the high-angle diffraction method applied to collagen orientation is not as sensitive as it is when applied to the apatite crystallites. It would be interesting to re-examine the material by the low-angle diffraction technique, which would demonstrate the orientation of the 640 Å periodic structure of collagen. Orientation in this larger repeating unit would undoubtedly constitute a better criterion for judging orientation in the collagen fraction, as the reflections from this unit seem to be more sensitive to the degree of orientation, and in fact can only be visualized in well oriented systems.

The relationship between bone age and crystallite orientation has been studied previously in adult bone formation (46). Since no evidence of alteration in the crystallite orientation was found in adult bone when new and old structures were examined, it was concluded that the age of the bone had no effect upon the ultrastructural characteristics. The fact that the collagen fibers in adult bone are relatively well oriented in the longitudinal axis of the bone, again favors the concept that the degree of fiber orientation determines that of the crystallites, but does not exclude the possibility that randomly oriented crystallites exist in the very first bone laid down.

Electron microscopic examination of human fetal bone (12) has indicated that the diaphyseal portions contain densely arranged crystalline components, comparable to those of adult bone, but that the epiphyseal areas possess only scattered foci of such dense mineral deposits, intermixed with areas of non-mineralized matrix. No attempt was made in the latter study to estimate the degree of crystallite orientation or the size of the particles.

Recently Clark and Iball (25) reported that they were unable to find signs of preferential orientation of the mineral elements in human fetal long bones from specimens younger than 4 fetal months. They attributed their results to the extremely small size of newly formed bone crystallites already described by others (63), as a consequence of which the crystallites could possess no effective longitudinal axis for orientation.

The latter findings are not in agreement with the present results, where, as early as the ninth to tenth week of fetal life, some areas of the fetal femur exhibit preferred orientation of the crystallites. This discrepancy probably results from differences in the experimental method employed. The results

of the present study suggest strongly that the areas of very young fetal bone which contain oriented crystallites are extremely small, and are therefore easily obscured in diffractograms which include adjacent areas of different anatomical orientation. It is therefore necessary to carry out repeated studies on various regions of such young bone, and to use as small an x-ray beam as possible in order to reduce the investigated area to a minimum.

The fact that no signs of orientation of the crystallites was found in most of the cross section is taken to indicate that the general direction of orientation tends to be primarily longitudinal. This fact would reduce the pattern of orientation in diffractograms of cross sections to a minimum and prevent its being visualized.

The absence of oriented apatite patterns in the newly-formed bone from the epiphyseal region of the femur may reflect an inability of the method to detect preferential orientation in these areas of extremely low mineralization, or it may indicate that only randomly oriented particles are present. If the particles of apatite are very small or are less perfect than those of older bone, or if the collagen matrix is less well oriented in a longitudinal direction than in other portions of the bone, the x-ray diffraction patterns of the epiphyseal region might yield erroneous information. However, as will be discussed later in detail, line-broadening analysis of the minerals in this region did not indicate the presence of much smaller crystallites, nor of imperfect ones, at least not to such a degree that the sensitivity of the x-ray diffraction method for orientation studies would be significantly decreased. Neither were the collagen bundles seen to be less well oriented in the very young bone. Therefore, it appears that the unoriented diffraction patterns obtained are indeed the result of random orientation of the bone crystallites in these epiphyseal regions.

The existence of unoriented crystallites in newly-formed bone may reflect specific properties of the crystallites themselves, or of the underlying organic matrix. Studies with the polarization microscope have confirmed previous histological findings (72, 94, 121) which demonstrated that the collagen fiber direction at the epiphyseal ends of the primary periosteal collar is well oriented in the long axis of the bone. If collagen orientation is responsible for the subsequent orientation of the mineral fraction, then this region should exhibit more orientation of the crystallites than any other part of the fetal bone. However, such is not the case, and thus orientation of the mineral must depend on factors other than the collagen orientation alone.

Arnold and Jee (6) showed that the optical activity of the collagen fibers changed just before and during the process of mineral deposition around them, and interpreted this finding as possibly representing chemical

alteration of the collagen molecule. It is well known that young bone contains more water than does older bone, and it may be presumed that at least some of this is bound to collagen. Under conditions of hydration, collagen is known to display alterations in its molecular structure (11, 71). This again suggests the existence of difference in the physical-chemical state of the ground substance in new bone as compared to old bone.

Our present knowledge of the organization and functional properties of the organic matrix are far too rudimentary to allow any more than broad speculation regarding its action on the bone mineral. The above examples, however, strongly suggest that among the properties possessed by this ill-understood organic complex is that of causing a preferential orientation of the inorganic compartment.

It is also possible, however, that certain properties of the inorganic crystallites themselves, especially their size and shape, might have an important effect upon their tendency to become preferentially oriented. A smaller crystallite size in very young bone has been suggested as an explanation for the increased physical-chemical and metabolic activity of this bone as compared to bone in a more mature condition (4, 32, 123). Electron microscopic evidence has provided support for this idea (98), by demonstrating the presence of larger crystallites in adult bone than in infant bone.

The results obtained by electron microscopy regarding crystallite size are not exactly comparable to the diffractometric line-broadening studies described here, since the first method provides information about very small and limited areas of bone, while the latter method provides data regarding the average particle size in a much larger volume of material. Despite this fact, however, the findings of the present investigation seem to be in good agreement with those of the electron microscopists. With both methods of attack it has been possible to demonstrate a smaller particle size in newly-formed bone.

It may be hypothesized that the smallness of the particles would have some influence on their overall degree of orientation. This idea has been supported by Jackson and Randall (63), who were able to observe in the electron microscope the very first crystallites deposited in osteoid matrix. These particles were found to be extremely small, with a diameter of less than 100 Å, and did not show signs of elongation in the c-axis. Neither was an orientation in the c-axis apparent by electron diffraction. In their extensive studies of collagen-crystal relationships in bone, Robinson and Watson (97) also demonstrated that the small crystallites in young bone lacked a long axis. However, electron diffraction of these crystallites revealed preferential orientation along the c-axis. It seems that the single

dissimilarity of results between these two investigations arises from the relative age of the material. In the case of the bone studies of Jackson and Randall, the authors were fortunate to be able to visualize the first mineral deposits in the matrix, while Robinson and Watson studied somewhat older samples.

One interpretation of the studies of Jackson and Randall suggests that, if an area of newly-formed bone consisted of masses of crystallites of extremely small size and without a pronounced longitudinal axis, the crystallites would not display orientation in the diffractograms. However, determination of the particle size of the mineral deposits in these areas of newly-formed human bone has not, in the present study, revealed the average crystallite size to be extraordinarily small. Moreover, if an area of new bone consisted of very small crystallites, this fact would have been noted in the line-broadening effect even in the microdiffractograms. Finally, if the shape of the crystallites in this region was such as to preclude any elongation in the c-axis, this fact would have been apparent as a line-broadening of the (00′2) reflection in particular. No such effect was noted in these studies.

The average crystallite length in bone from a 15 week-old fetus, at which time the actual femoral bone deposits are from 6 to 7 weeks old, has attained a value of approximately 160 Å. Full-term fetal femoral diaphyseal crystallites possess an average length of 220 Å. When consideration is given to the fact that these are average lengths, and that the bone of a 15 week fetus contains proportionately more newly-formed, small crystallites than does the full-term bone, it then appears that growth of the crystallites must be extremely rapid. This idea is supported by Jackson (64), who, in her electron microscopic investigations of newly-formed bone, was not able to detect the presence of intermediate stages between newly-formed, small, and non-elongated particles and those possessing the more typical c-axis elongation.

It thus appears that the size of the apatite crystallites in newly-formed fetal bone, although evidently smaller than those of older bone, probably does not play a major role in determining whether orientation will occur. It seems much more likely that the causal factors will be succesfully localized in particular physical or chemical properties of the organic matrix.

V. General Discussion

The present investigation has concerned itself primarily with the study of those dynamic processes associated with mineralization in the human fetal femur. The great difficulty in finding areas in other developing bones which possess sufficient size and structural continuity throughout fetal development has precluded extension of the quantitative studies to them. Even in the femur, requirements of the experimental techniques have limited the scope of these observations to particular, relatively large, and homogeneous microscopic structures. Despite this fact, however, comparison of the data obtained from measurements of the level of mineralization in the femur reveals excellent agreement with those obtained in control examinations of fetal skull bone and vertebrae in different stages of fetal development. This evidence of correlation, plus the probability that neither the organic matrix nor the inorganic fraction vary in their essential composition from one fetal bone to another, provides an adequate basis for assuming that the data obtained from fetal femur are representative of the fetal skeleton as a whole.

Observations made of femoral development have indicated that mineral elements are deposited initially in the form of calcium-hydroxy-apatite crystallites, whose size is less than that found in adult bone. With progressive growth and development, the total amount of mineral present increases rapidly, soon attaining an almost constant level that is characteristic of fully-formed fetal bone. The increase in total mineral content is accompanied by what appears to be a rapid and progressive increase in the overall crystallite size, and also by a progressively greater tendency for the individual crystallites to be oriented in the long axis of the bone. The final levels of orientation and crystallite size also seem to be characteristic of fully-formed fetal bone.

Comparative graphic plots of the relationship between mineralization, crystallite size, and fetal age (Figure 31) indicate that the mineralization level increases initially at a more rapid rate than does the crystallite size. However, it must be borne in mind that the level of mineralization has been measured on single well-defined microscopical structures, the age of which has been estimated with fairly high precision. Crystallite size

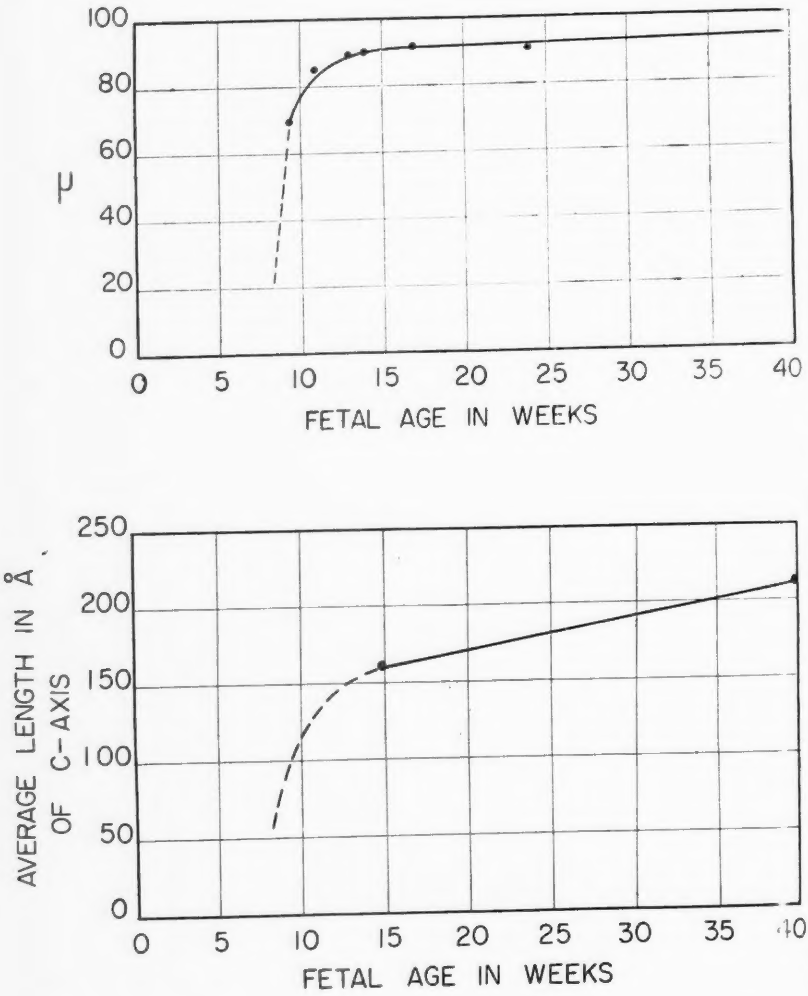


Fig. 31. Comparative plots of the rate of mineralization, expressed as the increment in mineral content in mid-diaphyseal cross sections (top), and the rate of increase of crystallite size, expressed as the increment in the long dimension of the crystallites (bottom), as related to fetal age.

determination, on the other hand, has been carried out on relatively large samples representative of an average age only. For example, the pooled samples of 15-week-old fetal bone contained femurs taken from fetuses ranging in age from 13.5 to 16.5 weeks. Moreover, since the first mineral deposits do not appear in the femur until the ninth week of development, the age of the oldest crystallites present in this sample can be at most 7 to 8 weeks, while their average age is between 3.5 to 4 weeks. If, then, the first point on the crystallite size curve shown in Figure 31 (160 Å) is correlated to a bone age of approximately 12 weeks, i.e., 3.5 to 4 weeks after the first appearance of minerals in the bone, the initial slope of the curve becomes much more similar to that of the mineralization curve, and probably provides a more accurate measure of the rate of crystallite growth.

While it is perhaps not particularly surprising that the mineral content and crystallite size increase as the bone matures, the rapidity with which these activities occur is quite startling. Moreover, the fact that an almost constant and specific degree of mineralization and crystallite size is attained rapidly, suggests the presence of factors in fetal bone which closely control or govern these processes. What, then, is the nature of these factors?

The increase in mineralization observed in growing fetal bone can reflect either the addition of new crystallites, or increase in size of the particles already present, or both of these processes. The number of crystallite "seeds" which appear in a given submicroscopic area of growing bone seems to be determinded by properties of the organic matrix, and occurs evenly and simultaneously in that area (63). The rate of increase in mineralization of such areas would therefore depend entirely upon the rate of growth of the crystallite seeds. At the structural level of organization observed in the light microscope, on the other hand, the process of ossification seems to manifest itself as a fusion of many of these submicroscopic foci of mineralization. Since adjacent submicroscopic areas are not necessesarily in the same stage of ossification, some, indeed, containing no evidence of the presence of minerals (12), then the rate of mineralization at the microscopic level would be determined both by the rate of appearance of new seeds, as well as by their rate of increase in size. The similarity of the curves plotted in Figure 31, however, suggests that for the present sudies the rate of increase in crystallite size is more important to the observed increase in mineralization than is the rate of increase in the total number of crystallites. As a consequence, it would seem that the most important single factor involved in determining the final level of mineralization in fetal bone is the process or mechanism by which the ultimate size of the crystallites is limited.

Several alternative explanations of the factors which limit crystallite growth in bone have been offered. It is well known, for example, that the

apatite particles in bone have a much smaller size than that of apatite crystallites precipitated *in vitro*. It has been proposed (53) that this difference might be attributable to the presence of ions bound to the surface of the bone salt crystallites, particularly carbonate and citrate. This idea has been given support by recent studies (92), which demonstrated that the large-sized particles of apatite precipitated *in vitro* on collagen could be reduced to dimensions corresponding to those characteristic of bone by addition to the medium of small concentrations of carbonate and citrate.

A second explanation of the mechanism which might determine the ultimate size of bone crystallites is based on the fact that formation of the apatite crystallites takes place at the expense of water, which is known to be present in excess in young bone. This water is partially consumed in the process of crystal formation and growth, for it is required as an integral part of the crystal structure (84). Simultaneously, it is also displaced from the tissue space which it formerly occupied by the progressive increase in crystallite volume. Ultimately the volume occupied by the crystallites attains such a magnitude that water is no longer readily available for continued crystal growth. This hypothesis seems to be logical, and it is in accord with the pattern of increase in crystallite size shown in the present study, in that it exhibits an initial rapid period of growth, followed by a progressive reduction in the growth rate, and ultimately cessation of growth. According to this concept, the final size of the particles would actually be determined by the number of crystallite seeds originally deposited in the organic matrix.

Consideration of the properties of the organic matrix have led to other explanations of the regulatory mechanism influencing crystallite growth, based particularly upon the molecular structure of collagen. The 640 Å banding of collagen has been seen to have a subperiod of approximately 200 Å. It has been suggested (19) that this periodic structure may constitute the governing influence upon the growth of bone crystallites, and thus determine the average 220 Å long dimension of the crystallites found in adult bone. According to this concept, then, the structure of collagen would be responsible for both the size of the crystallites as well as their physical orientation.

It has also been proposed (55) that the characteristic length of the crystallites results from the fusing together of smaller sub-units. This idea has been restated on the basis of electron microscopic investigations (98). If crystallite fusion constituted the normal mechanism of crystallite growth, however, the curves derived from the present study (Figure 31), which correlate crystallite size, level of mineralization, and fetal age, would certainly not bear such a close resemblance to one another. It should be noted, moreover, that the present findings do not support the explanation for

the high reactivity of newly-formed bone, as being a reflection of an increased available crystallite surface area, resulting from a larger number of particles. For this assumption would require the existence of crystallite sub-units, the number of which would then have to be progressively reduced as bone growth ensues. The observations in the present study, however, do not indicate that any significant reduction in particle number occurs during growth. An alternative explanation for at least a part of the increased reactivity of new bone could be based on the very rapid growth rate of the young crystallites, and the consequent increased incorporation into their structure of ionic materials. However, the physical-chemical process of surface recrystallization is increased in new bone (83), and thus must also be of great importance in increasing the overall reactivity of the mineral compartment of newly-formed bone. Also, ion-binding properties associated with the organic matrix under conditions of rapid growth may play a role in this process (83), but these are not yet fully understood.

It is most apparent from the above discussion that, although modern methods have provided much new information regarding the characteristics of bone salt, explanations of the dynamics of growing and adult bone cannot be based entirely upon considerations of the isolated inorganic fraction. The relationship between the minerals and the underlying matrix is far too intimate to allow this. It is only by the refinement of existing experimental methods, by the development of totally new ones, and by their vigorous application that we can hope to accumulate a similar volume of information about the organic matrix, and, as a result, be able to construct a final and integrated concept of the structure and function of bone.

VI. Summary and Conclusions

The recent development and application of biophysical methods of analysis, capable of providing detailed information regarding the submicroscopic structural and chemical characteristics of biological materials, has been of particular value in the study of bone, and has led to our current concept of this tissue as a dynamic and extremely important physiological system. To a great extent, however, such investigations of bone have been confined to the adult tissue, and thusfar have provided only a partial insight into the ultrastructural details of bone formation and growth.

The present investigation, therefore, has been undertaken in an effort to increase our knowledge regarding the structural and functional aspects of rapidly growing bone. Experimental emphasis has been placed primarily on quantitative and ultrastructural analyses of the mineral compartment, although additional information has been sought regarding the relationship of bone mineral to the underlying matrix.

The techniques employed have been those of quantitative microradiography, which measures the total mineral content in microscopic structures of bone, and of x-ray microdiffraction, which provides information relating to the crystalline and chemical nature of the bone mineral and to is physical orientation in the tissue. Details regarding the structure and orientation of the organic matrix have been investigated by means of polarization microscopy and x-ray diffraction methods.

The experimental objects employed in this study have been human fetal femurs, taken from fetuses ranging in age from 6.5 weeks to full-term. The choice of fetal bone has been based on the assumption that those changes in ultrastructure which are characteristic of all bones during rapid growth would be most evident at a time when the growth rate of the entire body is at its maximum. Moreover, it was hoped that the use of this material would also permit supplementary observations to be made on some of the specific details of human fetal bone formation and growth, our knowledge of which is rather limited.

This investigation has allowed the following conclusions regarding the formation and growth of human fetal bone to be drawn:

1. Newly-formed bone in the fetal femur possesses a very low degree of mineralization. From its very first appearance, however, the mineral component of this bone exhibits an x-ray diffraction pattern characteristic of calcium-hydroxy-apatite.

2. The mineral content of fetal bone increases rapidly during the three weeks immediately following its first appearance, but thereafter maintains an almost constant level up to the time of birth. The linear absorption coefficient, which reflects the degree of mineralization, has a value of approximately 85 in nearly all mature fetal bone, as compared with a figure for adult bone of about 95. However, certain portions of the fetal bone, i.e., the calcified cartilage cores of endochondral bone, the central cores of the periosteal bone layers, and the innermost portion of the primary periosteal collar (Grenzlinie), possess a higher degree of mineralization then does even adult bone, their linear absorption coefficient attaining a value of about 100.

3. Parallel to the rapid increase in mineral content in fetal bone, there occurs an increase in the long dimension of the apatite crystallites, which in newly-formed bone is very small. In full-term fetuses, this dimension averages 220 Å, which is approximately the same as the average value for adult bone. In fetal samples whose average age is 15 weeks, on the other hand, the crystallite long dimension averages approximately 160 Å. The initial increase in crystallite size appears to be very rapid, and its rate is strikingly similar to that of the increase in mineral content.

4. The first crystallites formed in fetal bone, are not oriented with respect to the underlying collagenous matrix. Between one and two weeks after the appearance of the crystallites, however, they exhibit a distinct orientation in the long axis of the collagen fiber bundles. The factors which determine the crystallite orientation seem to be related to the organic matrix rather than to the crystallites themselves.

5. At the ultrastructural level of organization, the rapid and progressive increase in the degree of mineralization of fetal bone seems to be related primarily to the increase in size of the small apatite crystallites during bone growth. The rate of increase in mineral content thus appears to be a function of the rate of increase in crystallite size, while the ultimate level of mineralization attained in a given ultrastructural area of fetal bone is governed by those factors which cause crystallite growth to cease. These latter factors appear to be properties of the organic matrix rather than of the crystallites, and their nature is not yet understood.

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BIOPHYSICAL ANALYSES
OF THE FORMATION AND STRUCTURE
OF HUMAN FETAL BONE

by

Göran Wallgren

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